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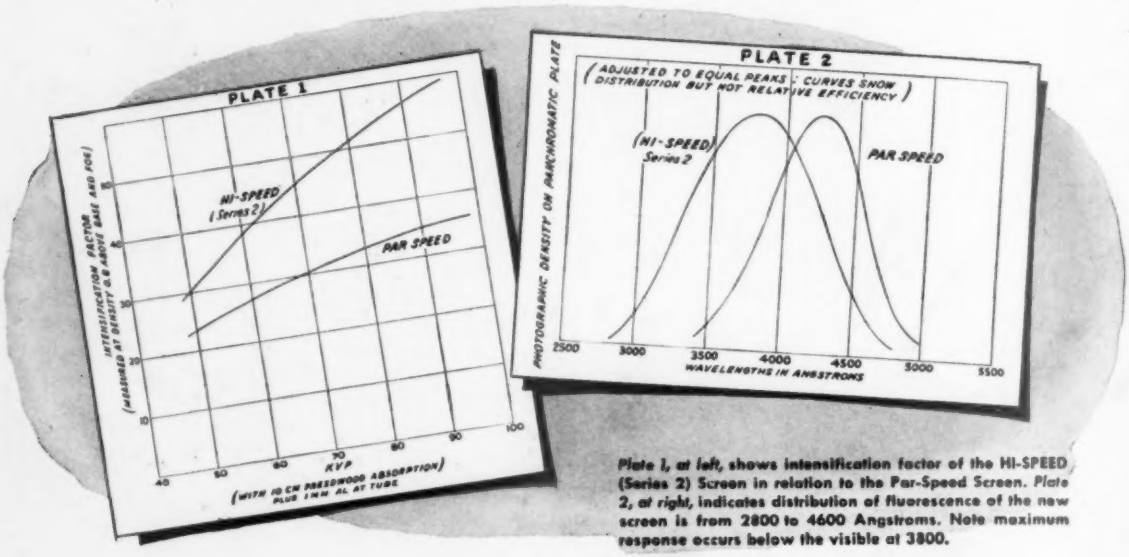

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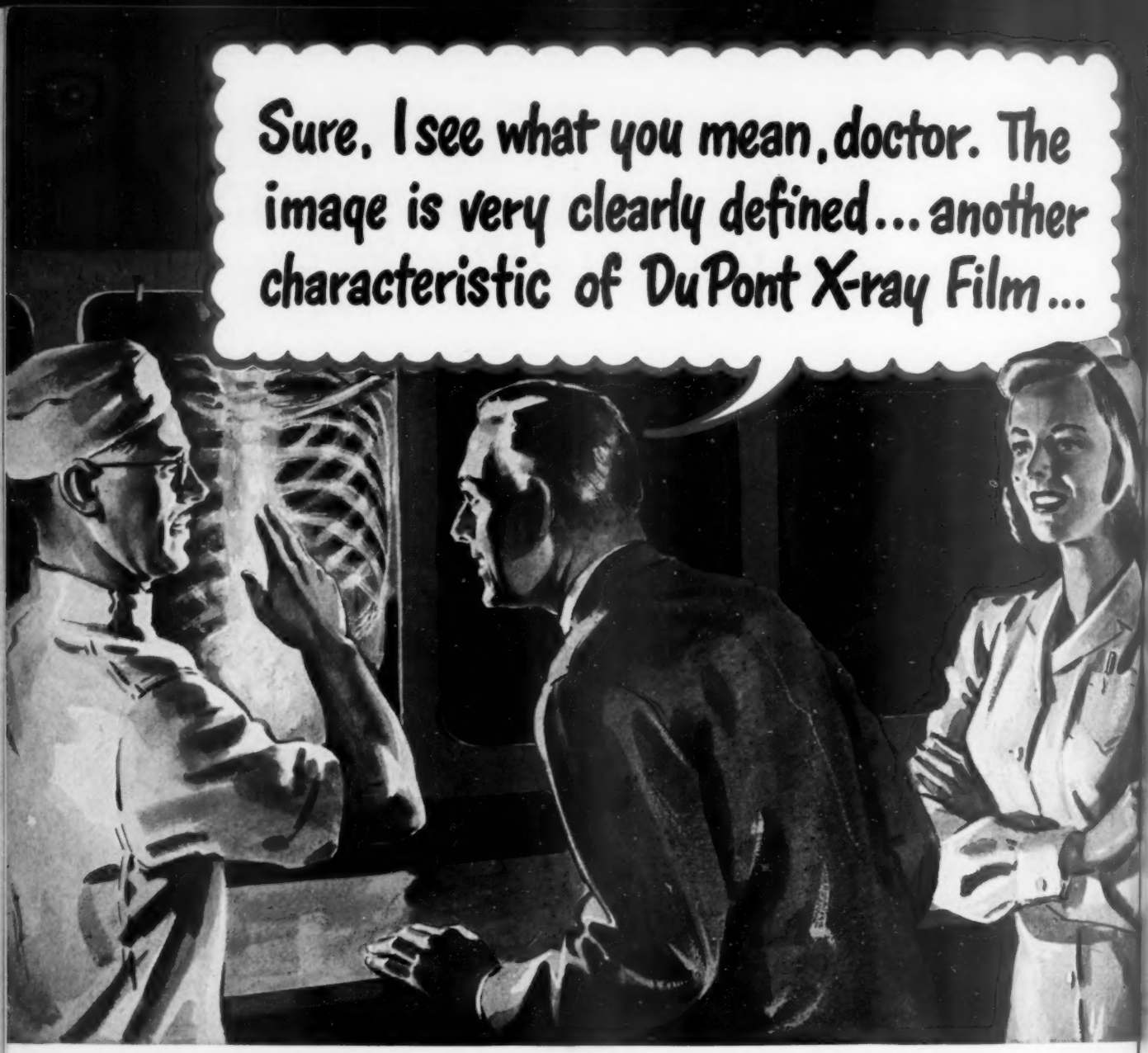

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ROBERT S. STONE
JANEWAY LECTURER, 1947

THE AMERICAN JOURNAL OF ROENTGENOLOGY AND RADIUM THERAPY

VOL. 59 JUNE, 1948 No. 6

NEUTRON THERAPY AND SPECIFIC IONIZATION

JANEWAY MEMORIAL LECTURE*

By ROBERT S. STONE, M.D.
University of California Medical School
SAN FRANCISCO, CALIFORNIA

MR. PRESIDENT, members and guests of the American Radium Society, I want to thank the Society for the honor of being selected to deliver the 1947 Janeway Lecture. It is a great privilege to be allowed to participate in this means of remembering Dr. Janeway. I never had the pleasure of knowing Dr. Janeway personally, but his work and the contributions he he made to our specialty, both directly and through those whom he inspired, are known to all of us. Were he here today, he would be keenly interested in the results of a type of radiation therapy that was not known in his active days.

Neutrons were identified in 1932. Intensive treatment of human cancer with them was started in 1938 and continued until early in 1943. More than four years have passed since the last treatment was given. I hope, by a review of the results of those treatments and of animal experiments, to show that:

1. The theoretical reasons for testing the biological effects of neutrons were sound;
2. The practical reasons for an early trial of the effects on human cancer, while appearing sound, did not envisage the late effects;
3. The late effects from the irradiation of animals with neutrons are greater in proportion to the early effects than would be expected from previous experience with such effects from irradiation with roentgen rays;
4. The rate of administration of any radiation plays a bigger role than most of us have believed probable; in other words, the distribution of ions in "time" as well as in "space" is significant;
5. Neutron therapy as administered by us has resulted in such bad late sequelae in proportion to the few good results that it should not be continued;
6. The late results from the use of neutrons should serve as a warning to those proposing to use protons, multimillion volt beta rays and multimillion volt roentgen rays in the treatment of human cancer.

NEUTRONS AND FAST NEUTRON BEAMS

Neutrons, as you all now know, are particles of matter of the same weight as the

* The twelfth Janeway Memorial Lecture, delivered at the Twenty-ninth Annual Meeting of the American Radium Society, Atlantic City, N. J., June 9–10, 1947.

nuclei of hydrogen atoms. They have no electrical charge. They do not ordinarily exist free in nature, but are part of the nucleus of all atoms except those of hydrogen. They may be obtained by knocking them out of atomic nuclei by bombardment with high energy photons or atomic particles. The method used at the University of California to obtain a beam of fast neutrons has been described on several occasions.[1] The cyclotron devised by E. O. Lawrence was used to give multimillion volt energy to deuterons which struck a beryllium target. From this target neutrons came forth with great energies. Aebersold[2] developed a collimating device such that clean-cut beams of varying sizes could be obtained.

Because of the structure of the cyclotron the beam of neutrons came out horizontally. This type of beam is very difficult to use as any of you know who have had experience with fixed horizontal beams. When patients have to lie on their sides for long treatments they tend to slip out of position. Moreover, the contents of the body cavities assume unusual positions when patients are placed on their sides. This handicap contributed some share to our bad results. The physical arrangement for treatments has been described in previous publications dealing with the early effects.[1,12,13]

MEASUREMENT OF NEUTRON RADIATION

Among the first problems to be solved was how to measure neutrons so as to be able to reproduce exposures and to compare results with those from other types of radiations. An "absolute" unit of measurement, such as the roentgen, was not, and still is not, available. However, since ionization results secondarily from the absorption of energy from neutrons, the same thimble chambers as are used to measure roentgen rays can be used, but the readings do not have the same significance. We used the 100 r chamber of the Victoreen condenser r-meter as made in 1938, but we called the units on the scale n units instead of roentgens. This provided a means of reproducing exposures. Aebersold and Anslow[3] determined experimentally that the energy absorbed in tissue was approximately the same from a free air exposure of 1 n as from one of 2.5 r, the neutrons being generated by 16 mev and the roentgen rays by 220 kv. Parker has suggested the use of the term rep (roentgen equivalent physical) to express tissue doses for radiations that cannot be measured in roentgens. One rep means that the energy absorbed per gram of tissue is the same as that from an exposure of 1 roentgen. On this basis, 1 n = 2.5 rep. The advantage of this unit lies in the fact that biological effects can be compared on the basis of similar energy absorption from various radiations rather than on the basis of arbitrary units. In most of the early literature and many recent publications, the neutron and roentgen-ray exposures required to produce the same biological effect are compared by the r/n ratio. Since it usually requires more roentgens of roentgen rays than n units of neutrons, neutrons are said to be more efficient. This is somewhat like saying that because it takes 12 inches of an inch rule and 1 foot of a foot rule to reach between two points, the foot rule is more efficient. The units must be physically equivalent if proper comparisons are to be made. Whenever doses of neutrons are specified in n units, they can be multiplied by 2.5 to bring them to reps and thereby placed on a basis of equal energy absorption per unit for better comparison with doses of roentgen rays expressed in roentgens.

Gray,[6] after using several methods of measuring neutron radiation, decided to express exposures in "energy units." He defines his unit of dose as "that amount of neutron radiation which produces an increment of energy in unit volume of tissue equal to the increment of energy produced in unit volume of water by one roentgen of gamma radiation." His unit is essentially the same as Parker's rep.

RELATIVE BIOLOGICAL EFFECTIVENESS

Before any treatments of cancer patients were initiated, a considerable amount of biological experimentation was completed

and a lot more has been accomplished since. In almost all of the investigations reported using a wide variety of cells and organisms it has been found that the *qualitative* effects of different radiations are indistinguishable from each other. Two exceptions should be noted. Spear and Tansley[11] found that neutrons cause more primary cell degeneration—as distinct from degeneration at the time of mitosis—than gamma rays, and Marshak[9,10] came to the conclusion that neutrons had more effect than roentgen rays on cells in the "resting" stage, both of these being qualitative changes. On the other hand, the *quantitative* effects—the effects produced by physically equivalent exposures—of various radiations have differed significantly.

The relative biological effectiveness of neutrons to roentgen rays can be expressed as the ratio of the number of roentgens of roentgen rays to the number of reps of neutrons required to produce the same biological effect. When this ratio is 1 the biological effect is produced by the absorption of the same amount of energy from both radiations. When it is greater than 1, the biological effect under consideration is caused by the absorption of less energy from the neutron beam than from the roentgen-ray beam; in other words, the neutron radiations are more effective per unit of energy absorbed. Applying this basis to the published results of various investigators it is found that the relative biological effectiveness varies greatly from one test object to another. Lewis[8] found that the relative biological effectiveness for the inhibition of growth of chick embryo fibroblasts in tissue culture was 0.8, i.e. neutrons were less effective than roentgen rays. Zirkle and Lampe[15] found that the relative biological effectiveness for the inhibition by 50 per cent of hatching of *Drosophila* eggs varies from 0.76 for 1½ hr. eggs to 1.24 for 4½ hr. eggs, i.e. neutrons were less effective in the first case and more effective in the second case than roentgen rays. Axelrod *et al.*[4] found the relative biological effectiveness for the inhibition of growth of a mouse lymphosarcoma irradiated in vitro to be 3. Gray *et al.*[5] have recently reported the relative biological effectiveness for regression of mouse tumors irradiated in vivo to be 20, but they used neutrons with lower energies than most American investigators have used.

It was thus obvious quite early, and has become more so recently, that the biological effectiveness of neutrons relative to roentgen rays varied from one tissue to another. The great question in regard to the treatment of human cancer was, would the effect on cancer cells relative to that on normal cells be greater for neutron than for roentgen-ray radiations? In 1938 we felt that no amount of animal experimentation would answer this question. In the tumor service of the University of California Hospital Out-Patient Department there were, as in all clinics, a number of patients with incurable cancer. It was felt that the prospect of helping these patients was sufficiently great to justify trying the effects of irradiation with neutrons. The early results of those treatments have been published[12,13] and here only a few pertinent facts will be reviewed.

It was found that a threshold skin reaction closely paralleling that from roentgen rays could be produced on the forearm with an r/n ratio of 7 for 8 mev neutrons and 6 for 16 mev neutrons, i.e. the relative biological effectiveness was 2.8 and 2.4 respectively. The relative biological effectiveness for a first degree erythema of face from a single dose was 2 (r/n = 5/1). But we found also that increasing the dose of neutrons required to produce the first degree erythema by 50 per cent did not cause an epidermolysis, whereas we would have expected that reaction from such an increase of dose of roentgen rays. Hence, at that time we should have been warned that the ratio of doses required was not the same for all effects on the skin. In other words, the relative biological effectiveness of neutrons to roentgen rays was somewhat less for the more severe reaction. It will be shown by results reported later in this lecture that the relative biological effectiveness of neutrons as judged by late skin and

subcutaneous reactions is much larger. Thus, even on human skin and subcutaneous tissue one cannot extrapolate the relative biological effectiveness from one reaction to another.

SPECIFIC IONIZATION AND BIOLOGICAL EFFECT

The reason for these variations in biological effectiveness is not known and no satisfactory theory has yet been propounded. While many facts are known, the correlation of them is not clear. Because the biological effects from roentgen rays of any given quality are proportional to the ionization in the tissues, it might be assumed that the effects are the direct result of the ionization. Since the amount of energy absorbed is proportional to number of ion pairs formed, it might be assumed further that a given biological effect would be produced by the absorption of a specific amount of energy per gram of tissue. However, every radiologist knows that more tissue roentgens are required to produce a given reaction when gamma rays are used than when roentgen rays generated by 200 kv. are used; yet a tissue roentgen of either one is supposed to represent the same number of ion pairs per gram and the same number of ergs absorbed per gram. When neutrons are considered still greater biological differences result from the formation of the same number of ion pairs or the absorption of the same number of ergs per gram.

Photons transfer their energy to electrons and these in turn cause the ionization. The number of ions produced along the path of an electron varies inversely with the velocity (energy) of the electron. High energy roentgen rays produce more high energy electrons and hence a greater distance between the ions produced. The number of ion pairs produced per unit length of the ionization tracks is called the specific ionization. It is therefore an inverse measure of the spacing of the individual ion pairs along the tracks of the ionizing particle.

Neutrons transfer their energy in tissue mainly to protons and these in turn cause ionization. Since the proton has a much greater mass than the electron, its velocity is much less than an electron having the same energy, and therefore the density of ions along its path is much greater, but the path is shorter. From these facts, it is obvious that even when the total ionization in a gram of tissue is the same from roentgen-ray and neutron radiations the spatial distribution of the ions within the gram will be different. Many tissue cells or protein molecules will be penetrated by the electrons, but few of them will have more than one or two ion pairs produced in them, whereas only a few will be penetrated by the protons, but those few will have many ions produced within them. If only one or two ions per cell are required to produce a given effect roentgen rays should be more effective, but if many ions are required, neutrons should be more effective. After a comprehensive review of the literature, Zirkle[14] concluded that in producing most types of acute injury to the higher plants and animals a radiation is likely to be more effective the greater the number of ion pairs produced per unit length of the track of the ionizing particles. Stated in another way, the greater the specific ionization, the greater the biological effectiveness on higher animals.

It must be remembered that the process of ionization accounts for only about one-half of the energy transferred from the radiation to the tissues. One of the other processes that occurs is the excitation of molecules which may result in the breaking of chemical bonds. Too little is known about the role that this plays in producing biological effects. It may well be that such energy transfer does not always run parallel to ionization and hence to measurements in roentgens or reps. There are other chemical changes induced by irradiation such as the initiation of the chain reaction of the combination of many hydrogen ions with chlorine resulting from the initial ionization of only one hydrogen molecule in the presence of chlorine. I am incapable of discussing these phenomena further. They are

mentioned because I did not want to leave you with the impression that we must study only the spatial distribution of ions in an attempt to explain the difference in effectiveness of various radiations on biological materials.

PILE NEUTRONS

With the advent of the self supporting chain reacting nuclear fission piles, interest in the effects of radiations, and especially of neutron rays on biological material, extended far beyond the circle of therapeutic radiologists. The safety of thousands of workers became involved. The energy of the neutrons from fission is much less than that of most of those produced on cyclotrons. Gray and others had shown that neutrons with energies of 1 to 3 million electron volts are more biologically effective than those with greater energies. The results of the mass biological research done on the Manhattan Project are gradually being revealed and a great many more are soon to appear in the National Nuclear Energy Series. Some results of experiments done by Henshaw, Riley and Stapleton[7] in collaboration with Zirkle, Curtis and Cole at the Clinton and Metallurgical Laboratories of the University of Chicago have a direct bearing on the subject we are considering.

While studying acute lethal effects from single doses of gamma rays they found that when the radiation was given at the rate of 3 r per minute it required 1,200 r to kill 50 per cent of the mice whereas when it was given at the rate of 30 r per minute it required only 840 r. The same strain of mice was used in both experiments. In another experiment, they found that exposing mice over long periods to 51.6 r one day per week had more effect on reducing their life span than giving 8.6 r each day for six days per week (i.e. 51.6 r per week). They concluded that the distribution of ionization in "time" varies the biological effect in a way similar to the distribution of ionization in space.

They used several reactions to study the comparative effects of neutrons and roentgen rays. One of the most sensitive was a reduction of the life span of the mouse. Mice exposed to radiations might show no other detectable effect than a shortening of their life span. Using this as an indicator they found the relative biological effectiveness of pile neutrons to gamma rays to be 3.6 when single large doses were used and 14 when daily periodic small doses were used. This is the largest difference in effectiveness that they found and would seem to indicate that the cumulative effect of repeated doses of neutrons is much greater than that of repeated doses of roentgen rays. The range of doses used varied around 0.25 n of neutrons and 8.6 r of gamma rays per day.

In studying the effects on the peripheral blood, on the weight of the animals and on the repression of leukemia in a leukemic strain (C58) they found the relative biological effectiveness of the pile neutrons to gamma rays to vary around 3.4. Thus, they as others, found that neutrons are more effective than gamma rays for equal amounts of absorbed energy and that the ratio of effectiveness varied for each reaction studied.

FAST NEUTRON THERAPY

This brief survey of the vast biological field has shown how difficult it is to decide from animal experiments how to proceed to clinical experimental therapy. We started with the knowledge that for epilation of rabbits 1 n = 4 r and that for acute lethal effects on mice 1 n = 4 r and thought that if we used one-fourth as many n units as we were accustumed to use roentgens, we would be on safe ground. We soon found that for the threshold skin reaction on the human forearm 1 n = 6 to 7 r. Had we known then that for the chronic effect of shortening the life span 1 n = 35 r or that for some in vivo experiments with mice tumors 1 n = 50 r (Gray[5]) we might never have started.

From September 26, 1938, until June 20, 1939, we treated a total of 24 patients on the 37 inch cyclotron using 8 mev deuterons to produce the fast neutrons (Table

1). One of those patients is still alive. He had a carcinoma of the left upper lobe of the lung with metastases to the left supraclavicular region as proved by biopsy. He had roentgen therapy following the neutron therapy. He still has a hard mass in his neck but he has been healthy and active for the eight years since treatment.

In November, 1939, the cyclotron with 60 inch pole faces and giving deuterons with 16 mev of energy was ready for operation in the Crocker Radiation Laboratory. The apparatus and its operation were described by Aebersold.[1] The methods of treatment, early reactions and short term results were presented by Stone and Larkin.[13] The treatment of patients was continued until February, 1943, at which time Larkin entered the Naval Reserve, I had joined the Plutonium Project and the cyclotron itself was needed for the Manhattan Project. It is now more than seven years since treatments were started and more than four years since the last one was given. Sufficient time has elapsed to make it profitable to study survival periods and late effects.

TABLE I

FAST NEUTRON THERAPY

37 INCH CYCLOTRON OPERATING AT 8 MEV	
Treatment Period September, 1938 to June, 1939	
No. patients treated	24
No. patients surviving 8 years	1
60 INCH CYCLOTRON OPERATING AT 16 MEV	
Treatment Period November, 1939 to February, 1943	
No. patients treated	226
No. patients alive January 1, 1948	17
Surviving over 7 years	5
Surviving over 6 years	7
Surviving over 5 years	4
Surviving 4 yr., 11 mo.	1

In evaluating the results, several facts must be borne in mind. The patients selected for treatment with fast neutrons were, with one single exception, those considered incurable by any known means. Many of them had had previous treatment by means of surgery, roentgen rays or radium, or some combination of those methods. In some patients all of the known areas of involvement were not treated because the disease was too extensive; treatments were given to see what response would result in the area treated. The plan of treatment varied as experience was acquired. All of the treatments on the 60 inch cyclotron were given by the fractionation method and where possible by cross-fire techniques. The rate of administration varied around 5 n per minute. The cyclotron operated erratically, making it necessary to vary the rate of administration, the daily doses, the number of fields treated per day, the total doses and the number of days between the first and last treatments. Few if any patients received their treatments exactly according to the method planned. However, no treatment was considered complete unless a good erythema was produced and in the majority of cases some degree of epidermolysis was produced. Many radiologists consider that we overtreated rather than undertreated the patients.

The total number of patients treated on the 60 inch cyclotron was 226 (Table 1). One patient was treated on both cyclotrons and is included in both tables. For various reasons, both physical and mental, 31 of the patients did not complete their courses of treatments. A few had only one treatment but we have included every one who was accepted for treatment. On January 1, 1948, seventeen were alive, all but one, who lacked only one month, having lived more than five years from the day of his first treatment. Thus, 7.5 per cent of the total number survived five years or more. I believe that the average five year survival of an unselected group of patients whose cancers are not treated or not effectively treated is about 5 per cent. However, since the patients we treated were considered incurable and many had had other forms of treatment before coming to us, they would not be expected to survive as long as those in an unselected group.

PATIENTS NOW DEAD

The survival time of those patients who are now dead will be considered first. Table II shows the statistics according to the anatomical site of the lesions treated. The number of patients with lesions arising in any one area was not great. Patients with all kinds of malignant conditions were accepted in an attempt to give neutron therapy a wide trial. In general, the greatest shortest of those living through a complete series, one month and a half. Those patients with primary intrinsic lesions survived slightly longer than those with extrinsic ones, but the difference was very slight. As was reported before,[13] the persistence of necrotic ulcers of the larynx when the gross tumors disappeared was a serious complication. In 7 autopsy examinations, no tumor cells were found in the treated areas, but in

TABLE II

16 MEV NEUTRON THERAPY
Survival period of cases now dead
January 1, 1948

Location of Lesion	Total No. of Patients	No. Treated Completely	Average Survival	No. Treated Incompletely	Average Survival
Larynx	16	12	9 mo.	4	4 mo.
Pharynx	11	10	7 mo.	1	1 yr. 6 mo.
Tongue	18	15	7 mo.	3	4 mo.
Mouth	13	13	6 mo.		
Buccal mucosa	7	6	1 yr. 7 mo.	1	6 mo.
Lip	9	9	8 mo.		
Neck	20	19	9 mo.	1	1 yr. 11 mo.
Parotid gland	6	6	10 mo.		
Skin	8	7	1 yr.	1	10 mo.
Esophagus	8	7	4 mo.	1	2 mo.
Stomach	5	4	8 mo.	1	4 mo.
Colon and rectum	12	10	9 mo.	2	2 yr. 7 mo.
Anus	2	2	5 mo.		
Breast	11	9	1 yr. 4 mo.		
Prostate gland	24	24	2 yr. 8 mo.		
Brain	13	10	1 yr.	3	1 yr. 2 mo.
Lung	10	8	8 mo.	2	3 mo.
Miscellaneous	16	8	10 mo.	8	5 mo.

response to neutron therapy occurred in those lesions that ordinarily respond to roentgen therapy. Squamous cell carcinomas were affected considerably while adenocarcinomas of the stomach and intestines were altered very slightly if at all.

Larynx: There were 16 patients with malignant lesions of the larynx, 13 of whom had squamous cell carcinoma. Twelve patients had definite metastases and the others had such marked extension that one could not distinguish between the extension and metastases. The longest survival period was one year and seven months and the all there were ulcers showing no tendency to heal.

Pharynx: Included under pharynx are patients with lesions arising in the nasopharynx 7, in the hypopharynx 2, in the oropharynx 1, and in the tonsillar fossa 1. The persistence of non-healing painful ulcers was a factor in causing the short survival periods. The only patient surviving more than a year was a Chinese male who stopped coming in for treatment before the planned series was completed. He had a transitional cell carcinoma that ceased growing for a considerable period. Two

other patients with transition cell carcinomas survived for shorter periods than the average of the whole group.

Tongue and Mouth: None of the patients with primary lesions arising in the tongue and inside of the mouth lived very long in spite of some remarkable tumor regressions. As was to be expected, the patients with epidermoid carcinoma of the buccal mucosa survived longer than the others, some of them with apparent disappearance of the primary lesion and satisfactory healing. One patient lived nearly four years, one two and a half years and 1 one year and two months.

Neck: All patients treated for metastases in the neck only, the primary lesions having been controlled by other means of therapy, are grouped together. When reporting on the early results, we thought the response of metastatic lesions in the neck was very satisfactory. The relatively short survival time of this group clearly indicates that the initial response did not mean a cure.

Prostate Gland: The 24 patients with carcinoma of the prostate gland would appear, from the survival statistics, to have profited the most from their treatments. The introduction of hormone therapy and of orchiectomy in the management of many of these patients makes it difficult to evaluate the effect of neutron therapy on their survival. Of those dead, 5 lived more than four years and 6 others more than three years. The shortest survival time was nine months and the average for the 24 was two years and eight months. Twelve of them are known to have had metastatic lesions at the time of death. The damage of the normal tissues due to the radiation reactions was such that none of them lived comfortably. Six of them are known to have had persistent ulceration of one or more of the treated areas.

The miscellaneous group consists of patients with the following types of lesions: recurrent adenocarcinoma of the ovary 1; retroperitoneal metastases from a carcinoma of uterine cervix 1; abdominal metastases from a carcinoma of the testicle 1; retroperitoneal sarcoma 3; osteogenic sarcoma 2; sarcoma of chest wall 1; squamous cell carcinoma, metastatic in axilla 1; lymphosarcoma 1; myeloid leukemia 1; and Hodgkin's disease 1. None of them showed any unusual results as can be seen from the survival time.

Concerning the other groups of patients, little more can be said than is revealed by the statistics in Table II. Most of the squamous cell cancers of the lip, skin, esophagus and anus decreased in size and even

---

EXPLANATION OF COLOR PLATE

FIG. 1. Acute reaction, thirty-eight days after starting treatment. Treated through two opposing lateral fields three times a week, the total dose being 500 n to each field in forty-eight days. The black appearance of the crusts is due to the application of tannic acid.

Fig. 2. Chronic reaction, five years after treatment. Same patient as Figure 1. Note the blotchy atrophic skin, the absence of subcutaneous fat pad and the contraction of the scarred area.

FIG. 3. Chronic reaction, three years after a total dose of 673 n in twenty-four days. Note the blotchy atrophic skin. This patient has great difficulty in opening her mouth more than 1 inch.

FIG. 4. Chronic reaction, five years after a total dose of 500 n to each field in a period of twenty-nine days. The left buttock here shows ulceration. Later the center of the right scar broke down. Note the contraction of the tissues, telangiectatic vessels and atrophic skin. On palpation the tissues were hard down to and through the muscles.

FIG. 5. Chronic reaction, three years and four months after a total dose of 400 n to each field in fifteen days. Note the atrophic skin, telangiectasia and contraction of the central part of the fields causing a concave appearance that was not present earlier. Also, note the absence of subcutaneous fat.

FIG. 6. Chronic roentgen-ray reaction, seven and one-half years after treatment with 200 kv. roentgen rays, the total dose per field being 4,283 r (skin) in thirty-three days. Compare Figures 4 and 5. Note that the skin itself is atrophic and telangiectatic, but there is very little, if any, contraction and no depression because the subcutaneous fat has remained. On palpation the skin itself felt hard, but it was not bound down to the underlying muscles.

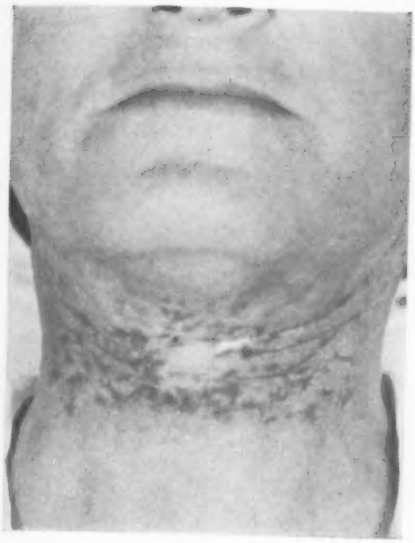

FIG. 2

FIG. 1

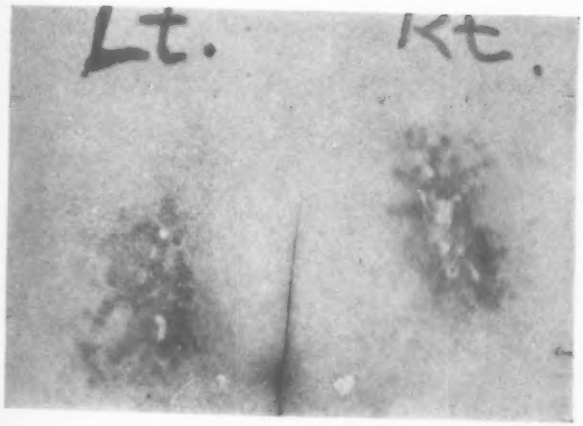

FIG. 4

FIG. 3

FIG. 6

FIG. 5

the metastases in lymph nodes and bone seemed to be controlled when seen shortly after treatment. In some cases no cancer cells could be found by the pathologists in sections from the treated areas. In nearly all of the patients the damage to the normal tissues was great. The adenocarcinomas of the stomach, colon and rectum decreased somewhat in size following treatment but did not disappear.

The date of the death of all patients is known but unfortunately because the war caused the two principal investigators to leave and put a heavy load on those remaining, and because many of the patients did not live in or near San Francisco, autopsies were often omitted and the cause of death was often not established. The short survival periods, however, indicate that the patients were not cured. We know that many of the patients developed severe complications as a result of the treatments.

PATIENTS STILL LIVING

The present condition of those patients still alive should furnish the best information on which to judge the value of neutron therapy. In Table III the patients still alive on January 1, 1948, are grouped according to the location of the primary lesion and the average survival time is given. If patients are to be kept alive by any method of therapy, their condition several years after the treatments is a matter of great importance. Hence the histories of these patients will be given in greater detail.

Larynx: The patient with the laryngeal lesion was a salesman, aged fifty-eight, whose lesion was localized in the right vocal cord, with some fixation. He was the only patient treated with neutrons who might have been cured by roentgen rays, radium or surgery—the only exception to our rule. The biopsy diagnosis was squamous cell carcinoma. He had had no previous therapy and chose to be treated with neutrons. Starting on March 5, 1941, he was treated through two opposing lateral fields, each 7 by 7 cm. in size. Nineteen treatments were given in forty-eight days, with a total dose to each skin surface of 500 n. On the basis of 1 n = 6 r obtained from the threshold skin tests, he received a dose to each side equivalent to 3,000 r (skin) of roentgen rays generated by 200 kv. A weeping epidermolysis appeared on the thirty-third day and lasted fifty-two days. Figure 1 shows the condition on the thirty-eighth day after starting treatment. The only difference between his reaction and that frequently produced by us with roentgen rays is that it was most severe over the anterior surface of the neck. The skin healed well but before a year had passed it became very blotchy in appearance and the subcutaneous tissues became indurated. Gradually the skin became more atrophic. Telangiectatic vessels appeared after the third year. Figure 2 shows the appearance five years after treatment. He now has fixation of the skin and subcutaneous tissues to the larynx—the whole area feeling very hard and containing numerous telangiectatic vessels. There are somewhat similar changes on the inside of the larynx to those described for the outside. The lesion promptly disappeared and has not recurred. The patient is content because he has his voice and has lived without evidence of his cancer for more than six

TABLE III

16 MEV NEUTRON THERAPY
Survival Period of Patients Still Living
January 1, 1948

Location of Lesion	Number of Patients	Average Survival
Larynx	1	6 yr. 10 mo.
Lip	3	5 yr. 10 mo.
Neck, metastatic	1	6 yr. 7 mo.
Parotid gland	3	6 yr. 2 mo.
Skin, metastatic	1	7 yr.
*Anus, primary	1	6 yr. 11 mo.
Breast, metastatic	1	6 yr. 2 mo.
Prostate gland, primary	5	6 yr. 1 mo.
Shoulder	1	7 yr. 1 mo.

* Incompletely treated. Surgical cure.

years. We are not content because we believe that if roentgen rays had been used he might have been "cured" with less damage to the normal tissues.

Lip: Three patients each of whom had an epidermoid carcinoma of the lip have survived.

The first case was a man, aged fifty-seven, who came with a recurrent lesion of the center of the lower lip with extension to the mandible and floor of the mouth and with a small hard submental node. He had had four separate radium treatments and three surgical procedures. In October, 1940, he was treated with neutrons through one field 10 by 10 cm. in size centering on the chin and including the whole remaining lower lip. He was given fourteen nearly equal treatments in thirty-two days for a total of 1,025 n (=6,150 r ?). An epidermolytic reaction appeared on the thirty-eighth day and lasted 143 days. When it healed the epidermis was so thin that it appeared as a thin sheen over the red subcutaneous tissue. All evidence of cancer disappeared. During the second year after treatment the area below the lip ulcerated and the mandible started to slough. In the third year, the mandible, chin and all tissue from the treated area were removed surgically. The pathologists could find no cancer. The plastic surgeons are slowly rebuilding his face. It is now over seven years since his treatment. While his cancer was cured, he has had seven years of great discomfort. Radical surgery at the start would have been better.

The second of these 3 cases was a man, aged seventy-two, with an extension to the alveolar ridge from a previous epidermoid carcinoma of the center of the lower lip and large bilateral submaxillary masses. He had had roentgen therapy and two surgical procedures on his primary lesion. He was treated with neutrons at weekly intervals in January, 1943, through two opposing lateral fields each 7 by 7 cm. in size so that he received four treatments in twenty-two days to a total of 400 n to each side. Lysis appeared on the twenty-ninth day and lasted only seven days. When last seen he had atrophy and telangiectasis of the skin and fibrosis of the subcutaneous tissues. He also had a large submental fistula through which his tongue protruded and his mandible was sloughing. There was no gross cancer present. After five years and an equivalence of only 2,400 r (6×400 r) this man has very severe skin changes.*

The third case of this series had a large left submandibular mass that recurred after surgery. The primary epidermoid cancer of the lip had been "cured" by roentgen therapy. In January, 1943, he was treated with neutrons through one field 10 by 5 cm. in size directly over the mass. Three treatments were given in fifteen days at weekly intervals, 200, 200, and 100 n, to a total of 500 n. Epidermolysis was present on the twenty-third day and lasted over thirty days. The tumor disappeared slowly. The skin healed but in a year ulcerated. It healed again while being treated with radon ointment. Now, nearly five years later, he has no evidence of tumor, but the skin is atrophic, with telangiectasia, and the subcutaneous tissues are very hard. If 500 n=3,000 r so far as the acute reaction is concerned it is equal to many more in so far as the late reaction is concerned.

Neck: A female patient, aged fifty-four, had a biopsy from a mass 4 by 4 cm. in size on the left side of her neck. The pathologist's diagnosis was metastatic squamous cell carcinoma. No primary lesion was located. In June, 1941, she was given ten treatments with neutrons in twenty-two days to a total of 670 n through a portal 7 by 7 cm. in size. Epidermolysis appeared on the forty-third day and lasted eighteen days. Now she has thin dry atrophic skin with no subcutaneous fat, but with fibrosis. She has no evidence of cancer. She had some ulcerated teeth removed from just above the treated area, with no complications.

Parotid: Three patients who had parotid tumors have survived seven years eight

* Since writing this lecture I have received word of the death of this patient.

months, six years three months, and five years respectively. The first and third had mixed cell tumors and still have small masses that are not enlarging. The second one had a carcinoma recurrent after surgery and now has no evidence of it. All were treated through single portals directly over the parotid, the first patient receiving a total exposure of 425 n in ten treatments in thirty-five days; the second receiving 673 n in eleven treatments in twenty-four days; and the third 600 n in three treatments in fifteen days. The treatments to the first patient produced a dry desquamation only, those to the other 2, epidermolytic reactions lasting sixteen days and eleven days. All now have trouble with jaw movements. All have skin atrophy, absence of subcutaneous fat and subcutaneous induration (Fig. 3). The one receiving the largest dose developed an ulcer during the third post-treatment year which healed while being treated with radon ointment. The one receiving the smallest dose developed radiation osteitis and a draining sinus during the sixth post-treatment year. Thus, a dose of even 425 n given in 7×50 n plus 3×25 n fractions in an elapsed period of thirty-five days to a colored boy of nineteen years, resulted in too severe late changes in the skin of a usually resistant area.

Skin: The patient listed under "skin" was a man, aged sixty-nine, who had had a primary epidermoid carcinoma on the upper half of his left ear. The surgeons had removed the upper half of his ear. He came to us in December, 1940, with a hard mass 5 cm. in diameter and at least 1 cm. thick, under the skin and fixed to the deep structures immediately anterior to the area of excision. He was given four treatments of 75 n each and three of 100 n in eight days, a total of 600 n to a field 10 by 10 cm. in size. Epidermolysis began on the twenty-first day and lasted sixteen days. By the end of one year the skin was blotchy and telangiectatic vessels were appearing. Since then the skin has become very atrophic; the subcutaneous fat layer has disappeared; and all the tissues from the skin to the skull have become very hard. During the fifth year an ulcer appeared in the treated area but healed. The tumor disappeared before the acute reaction subsided and has not recurred. Both the immediate and late reactions to 600 n given in eight days were greater than I would expect from 3,600 r of roentgen rays generated by 200 kv. and given in the same way.

Anus: The patient with the squamous cell carcinoma of the anus was a woman fifty-five years of age who came for therapy in January, 1941. She had had previous treatment with roentgen rays and radium but the cancer was regrowing. After receiving five treatments of 50 n each in ten days she refused further irradiation and one month later submitted to an abdominoperineal resection. Some carcinomatous cells were found by the pathologist, but he said they were degenerating. She now has slight skin atrophy and telangiectasia, but since she had had roentgen and radium treatments one cannot say that the changes are due to 250 n of neutron radiations.

Breast: The patient listed under "breast" came to us with a hard nodule in the supraclavicular area. She had had a radical amputation of her breast for a comedo carcinoma, followed by a full course of irradiation by roentgen rays to the chest wall, axilla and supraclavicular area. In April, 1941, she was given ten treatments of 50 n each in twenty-seven days to a single field 10 by 10 cm. in size. The supraclavicular area is now so hard that it is impossible to tell whether any tumor remains. The skin is atrophied. The combination of treatments caused the late changes—but the nodule that appeared after the roentgen therapy disappeared after the neutron therapy.

Prostate Gland: Five patients who had carcinoma of the prostate gland were still alive on January 1, 1948. When treatments were started, 1 was forty-nine, 2 were sixty-one, 1 was sixty-three and 1 was seventy years of age. Four had had transurethral resections and one an enucleation of the

prostate. No metastases were known to exist but there was local extension beyond the gland in all of them. One has lived more than seven years, 2 more than six years and 2 more than five years. Two are known to have metastases. Three are known to have marked induration in the region of the prostate, but this condition has not altered for several years so far as can be told by palpation. Three have had orchiectomy and are taking diethyl stilbestrol. Two have had neither orchiectomy nor hormone therapy and are apparently free of metastases.

All were treated through three portals, one anterior through the pubic region 10 by 10 cm. in size, two posterior, through each gluteal region 10 by 15 cm. in size. Three were exposed to approximately 500 n to each field, 1 receiving sixteen treatments in forty-five days, 1 eleven treatments in twenty-nine days and 1 ten treatments in twenty-five days. All of these patients developed an epidermolytic reaction in all fields, the main difference being that it appeared sooner in the patient treated in the shortest time. The other 2 patients had three treatments each in fifteen days (weekly intervals), each field being exposed to a total of 400 n. These treatments resulted in erythematous reactions with no lysis except a slight amount in one anterior field. In spite of the different methods and the different primary reactions all 5 cases developed late changes which were detectable before one year had elapsed. The skin became blotchy, white, telangiectatic and adherent to the underlying tissues. The subcutaneous fat disappeared. The skin, subcutaneous tissues and underlying muscles in all areas became united in hard masses which shrunk as time passed and distorted the structures in and near the treated areas. The gluteal induration made sitting painful and walking difficult. The indurated pubic areas blocked lymphatics with a resultant edema of the penis and scrotum. The contraction of the tissues in the anterior fields resulted in distortion of the penis, since its base was involved. One of the patients who was exposed to 500 n per field developed an ulcer anteriorly during the second year and a necrotic ulcer in the left gluteal field during the fifth year. Each of these ulcers took several months to heal. Still later, the skin in the right gluteal area broke down and the resulting necrotic ulcer has persisted for about one year. Another patient who was exposed to 400 n developed an ulcer in the anterior field. At least 5 of the patients who are dead had developed very severe painful ulcers in fields treated with no greater doses than those reported above. Some of the changes are shown in Figures 4 and 5, but unfortunately illustrations do not show the induration.

Shoulder: The last patient to be reported is a woman who had a fibrosarcoma on her left shoulder that had regrown in the scar of a second surgical excision. When she came to us in November, 1940, the tumor was 3.5 cm. in diameter and 2 cm. thick. She was given fifteen treatments in thirty-four days to a single field 10 by 10 cm. in size, the total dose being 1,075 n. A severe epidermolytic reaction appeared on the fifty-seventh day and from that time on the skin never healed. The resultant painful ulcer progressed in spite of all types of treatment and eventually pieces of the scapula sloughed from the bottom of the lesion. Two years passed with no evidence of metastases. It was decided to remove the necrotic area by a shoulder girdle amputation. The pathologist found no evidence of tumor in the removed tissue.

DISCUSSION

Sixteen patients who received complete courses of treatment with fractionated doses of fast neutrons have been observed for more than five years. Thirteen of them had severe epidermolytic reactions in all the treated areas; 1 had epidermolysis in one of three fields; 1 had an erythematous reaction; and 1 had only desquamation. Three patients had epidermolysis in gluteal fields, 1 in a field over the shoulder and 1 in a supraclavicular field. Most of them there-

fore had severe early reactions and late changes were to be expected. Even when this fact is taken into consideration, the late changes are more marked than were expected.

To compare the reactions produced by fast neutrons with those produced by roentgen rays, similar regions must be selected. This limits the present study to very small groups or individual patients and patients vary greatly in their reaction to roentgen rays even when treated by identical techniques. In spite of this, some comparison seems desirable.

The patient who had carcinoma of the larynx received a total exposure of 500 n to each of two opposing fields in forty-eight days. To produce an acute reaction similar to his (Fig. 1) would require a total exposure of considerably more than 3,000 r (skin) of filtered roentgen rays generated by 200 kv. when given in a similar time. If this is true, then 500 n = >3,000 r or 1 n >6 r. If 4,000 r was the required exposure then 1 n would equal 8 r. The late changes in the patient treated with neutrons were very marked (Fig. 2). We have produced as severe early reactions in patients treated with roentgen rays, and at the end of five years they have shown only a little skin atrophy and no fibrosis. From these considerations it is apparent that because the r/n ratio is 6/1 for a threshold skin reaction it will not necessarily be the same for the epidermolytic reaction or for the late atrophy and fibrosis reaction. The relative biological effectiveness of the two radiations varies for each reaction even when they occur in the same tissue.

The reactions seen in the gluteal region emphasize the above conclusions. Very marked skin atrophy, loss of subcutaneous fat and fibrosis of muscles resulted from a total exposure of 400 n in fifteen days as shown in Figure 5. The acute reaction in this field had been a first degree erythema. The appearance of the right gluteal area of a woman who had been treated seven years earlier with a total exposure in thirty-two days of 4,283 r (skin) of roentgen rays generated by 200 kv. is shown in Figure 6. While her skin is atrophic, blotchy and telangiectatic, some subcutaneous fat remains, fibrosis is less marked and no contraction of the area has occurred. Admitting the inaccuracy of comparing single individuals of different sexes it might be said that 400 n produced much more marked late changes than 4,000 r, or the r/n ratio is greater than 10.

This report has been limited largely to a discussion of the survival periods and skin reactions; however, the reactions of the deeper tissues have also been severe. Persistent ulceration in the site of tumor regression in those patients who had lesions of the mouth, pharynx and larynx has already been mentioned. The regenerative ability of the normal tissues apparently was damaged by a dose of neutrons which was not great enough to kill all cancer cells in all patients. Some of the patients treated through the mandible developed radiation osteitis. When the treatments were given through the pelvis, the effects on the intestine were quite severe. One patient who has lived more than five years has had very little bowel control for the last two years. By digital examination and by roentgenographic means the rectum and lower portion of the sigmoid were found to be relatively rigid, with little power of contraction. These few examples of the types of internal damage indicate that the patients were thoroughly irradiated in the depths.

While survival is important, the condition of patients surviving is of equal importance. Eighteen of 249 patients treated by fast neutrons on both cyclotrons have lived from almost five years to more than eight years since starting their treatments. Eight are apparently free of cancer. Eight others have so much induration in the region of the original tumor that it is not possible to decide whether or not any cancer is still present in the primary site, but 2 of them have metatastes. The remaining 2 have persistent small masses. Three of the 8 cases who are free of cancer had the treated areas removed by surgery,

2 having no cancer cells and 1 having "degenerating" cancer cells in the removed tissue. While all 18 have severe late reactions, 12 of them have such severe changes that they are partially incapacitated. These results are not encouraging even though some patients have been kept alive.

SUMMARY AND CONCLUSION

1. The physical measurement of neutron radiations in air in units that can be translated to tissue doses comparable to tissue roentgens has been difficult. The n unit of exposure is physically equivalent to about 2.5 roentgens as judged by the amount of energy absorbed from a beam by tissue. In other words, 1 n = 2.5 rep (roentgen equivalent physical).

2. Gross and microscopic studies of mammalian tissues have shown little or no qualitative difference in the reactions produced by neutron and roentgen-ray radiations.

3. The relative biological effectiveness of various radiations, as judged by the amount of energy absorbed from the beam in producing a given reaction, varied greatly from one test object to another and from one reaction to another even in the same tissue.

4. In general, the relative biological effectiveness of radiations on mammalian tissue was greater the higher the specific ionization. Neutrons were more effective than roentgen rays per unit of energy absorbed by tissue. It was hoped, therefore, that they might be more effective in the treatment of human cancer.

5. Biological work on the Plutonium Project, and the human work here reported, shows that the relative biological effectiveness of neutrous compared to roentgen rays is greater for late than it is for early effects. Whereas, 1 rep of neutrons might equal 2.5 r of roentgen rays for a threshold skin reaction, it might equal 4 r for late skin effects and even 15 r for the chronic effect of shortening the life span by repeated daily doses.

6. Biological work showed that for some effects of radiations, the distribution of ion pairs "in time" played a part similar to that of the distribution in space. The rate of administration was not sufficiently weighted in the treatment of patients.

7. From a study of the patients treated with neutrons it is clear that cancer cells can be killed and patients "cured" of their cancer, but the difference between the dose required to kill cancer and that to acutely damage normal tissue is very small. The difference is even less when reactions occurring several years after treatment are taken into account.

8. Eighteen patients have been kept alive, but none of them are free from distressing late effects.

9. Anyone contemplating the use on patients of new radiations such as multimillion volt protons, beta rays and roentgen rays should study the relative biological effectiveness of them by late reactions as well as by acute early ones.

This study was made possible by the wholehearted cooperation of Professor E. O. Lawrence and his staff at the Crocker Radiation Laboratory in Berkeley, California. Throughout a large portion of the active period, Dr. John C. Larkin, Jr. assisted in the work. During the war years, Dr. B. V. A. Low-Beer observed the patients. Financial assistance for the clinical work was given by the United States Public Health Service through the National Advisory Cancer Council. The Crocker Radiation Laboratory building was a gift of the late Mr. W. H. Crocker and the follow-up of the patients has been aided by financial assistance from the W. H. Crocker Trust Fund.

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DOSAGE MEASUREMENTS FOR VARIOUS METHODS OF INTRAUTERINE RADIUM APPLICATIONS IN CANCER OF THE ENDOMETRIUM*

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INTRAUTERINE radium implantation is a widely recognized mode of treatment for carcinoma of the endometrium. In most instances it is depended upon almost entirely for the treatment of inoperable or constitutionally inoperable patients.[1,2,3,13] Some authors also advocate intrauterine radium as a preoperative measure for operable patients,[5,10,13] and a few rely upon it as the principal therapeutic measure in all cases, operable or inoperable.[7,8]

Application of radium for such treatments presents many technical problems. The exact location, size, or extent of the intrauterine lesion encountered is often quite impossible to determine on vaginal examination or curettage. Therefore, accurate placement of the sources for optimum effect is difficult. It is also difficult to be certain that intrauterine sources will stay where they are placed during the interval of treatment. Gross enlargements and irregularities of the uterine cavity, due to extensive lesions or concomitant fibroids in many cases, make accurate placement still more uncertain. Many clinicians, including Arneson, Crossen, Friedman, Healy, Heyman, Kaplan, Marin, and Schmitz, have described special techniques of implantation to overcome some of these uncertainties.[10]

The use of a small and nonflexible tandem is the simplest method for intrauterine radium implantation. The disadvantage of this method is that there is no accommodation to the length of the uterus. A longer tandem still does not adapt itself to the instances where one cornu may contain a small tumor or where the tandem may be deflected away from the base of a large tumor by irregularities of the cavity.

More complicated applicators and hysterostats, which cause the sources to assume "Y" shapes, or "V" shapes, utilize the available space of the endometrial cavity more fully and also are fairly certain to stay in the position applied. They are semi-rigid in their construction, however, and are not adaptable to many uterine irregularities.

Heyman's technique of packing the available space in each uterus with irradiators of various sizes seems most adaptable to the technical problems presented by cancer of the corpus uteri. The procedure usually demands rather extensive equipment and care in introduction. Adaptations of this method have been made to available radium supplies in several clinics in this country.[10]

In the present study an attempt is made to measure and compare the radiation distribution among several examples of methods of intrauterine radium implantation under standard conditions. The practical problems of irregularity of the cavity, shifting to placement of the sources, and so forth, have been eliminated in order to evaluate the effect of the spatial placement of the sources themselves. From such purely physical studies we have hoped to be able to draw conclusions as to the expected biological response from each type of implantation.

EXPERIMENTAL METHOD

The experimental method has been the utilization of a film method of dosimetry. This

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method has been qualified for the purpose by a preliminary work which explored the range, accuracy, and adaptability of the film.[9]

A. The experimental procedure involved the construction of a phantom consisting of many layers of Masonite presdwood. In the center of two square sheets of this material a hypothetical endometrial cavity was fashioned. This was a roughly triangular or "kite-shaped" space 1 cm. deep, 4 cm. wide, and 7 cm. in length. The air space was not filled with rice flour or other dense medium in the experiments, but remained constant for each tested set-up. A stack of presdwood sheets, 20 cm. square and 10 cm. high, was constructed. Then a 20 by 15 cm. sheet of film was placed flat upon the surface of this. The presdwood sheets containing the centered "cavity" were then laid over the film and the sources arranged inside the cavity in a set fashion. A second sheet of film was then placed perpendicular to the first at the midline of the long axis of the cavity and presdwood sheets built upon either side of this to a height of 10 cm. In this way the films were exposed in two planes in the phantom. The phantom measured at least 10 cm. in all directions from the centered cavity. The position of the film in relation to the cavity was marked by tiny pin pricks through the covering and emulsion of the film for reference.

B. The radiation sources used in this study were taken from the radium supply available for therapy in the Mallinckrodt Institute of Radiology. They consisted of:

3 capsules averaging 25 mg. in strength, 1.5 cm. in length, 0.25 cm. in external diameter and with a filter of 0.5 mm. platinum.

7 tubes averaging 12.5 mg. in strength, 2 cm. in length, 0.2 cm. in external diameter and with a filter of 0.5 mm. of monel metal.

25 cells averaging 1 mg. in strength, 1 cm. in length, 0.125 cm. in external diameter and with a filter of 0.5 mm. of gold.

Because of the lack of uniformity among the sources in the radium supply, it was necessary to use variations in exposure time to reduce the experimental combinations to the same equivalent as far as filter was concerned. In all the set-ups actual treatment conditions were simulated and additional filtration was added so that no source was used without the equivalent of at least 2 mm. brass or 0.5 mm. platinum. This also served to exclude any darkening of the films from beta radiation which would upset the calibration. The exposure times were so calculated that each arrangement was equivalent to 1,000 milligram-hours from sources having a filter of 0.5 mm. Pt. The variation in diameter of the sources was not taken into account in these calculations.[6]

The arrangements studied are described as follows:

Plan I: Short tandem: 3 short sources; 4.5 cm. active length. External dimensions 5.5 by 0.5 cm. Strength 75 mg.

Plan II: Long tandem: 3 long sources; 6 cm. active length. External dimensions 7.5 by 0.7 cm. Strength 75 mg.

Plan III: "Y" applicator; short tandem (75 mg.) as in Plan I plus two large capsules in the cornua, 2 cm. active length. External dimensions 2.5 by 0.7 cm. Strength 25 mg. each.

Plan IV: Hysterostat; long tandem (75 mg.) as in Plan II plus two small capsules in the cornua. 1.5 cm. active length. External dimensions 1.5 by 0.25 cm. Strength 25 mg. each.

Plan V: Multiple capsules total of seven large capsules 2 cm. active length. External dimensions 2.5 by 0.7 cm. Strength 12.5 mg. each.

Plan VI: Multiple capsules: Total of 13 small capsules.

a. 7 capsules: 2 cm. active length. External dimensions 2.5 by 0.5 cm. Strength 12.5 mg. each.
b. 5 capsules: 1 cm. active length. External dimensions 1.5 by 0.5 cm. Strength 5 mg. each.
c. 1 capsule: 1.5 cm. active length. External dimensions 2.5 by 0.7 cm. Strength 25 mg.

The decision to investigate the treatment plans mentioned above was ruled by several factors. Of course, the plans were limited by the radium supply and equipment at hand. Plans were simulated which would show the effect of an increasing number of these sources within a closed space. A similar alignment of the sources relative to the long axis of the space was maintained in all plans. Gray, Friedman and Randall[5] have shown the advisability of placing sources transversely in the uterine fundus and demonstrated the so-called "end-reaction" of radium tubes by photographic methods. In multiple capsule applications this transverse placement is attempted in nearly all cases and has been demonstrated by roentgenograms with the radium in place.[10] However, this refinement was not demonstrated in any of the plans studied in order to maintain simplicity and a reasonable order for comparison.

For each series of experiments and their calibration Defender Adlux film of the same emulsion number was used. The film was cut to size and sealed in double black paper envelopes in the dark room. After exposure all experimental

films and calibration films were developed together. The development factors were: temperature 68° C., developer Dektol, time 2 minutes. This procedure was carried out in a pan with careful constant agitation by hand development.

After drying of the film, it was marked with soft lead pencil to show reference points and grid lines. The density at specific points was read on a Marshall transmission densitometer. The scale on this instrument is logarithmic and extends from Do to D3. Calibration and experiments were carried out at an intensity which would utilize the mid-portion of this range for optimum accuracy.

The calibration of the film is shown in Figure 1. Here the smallest and strongest source available (25 mg., 1.5 cm. active length, 0.25 cm. distance, 0.5 mm. Pt filter) was placed flat against the film. The exposure time was for forty hours in air. The milligram-hour exposure for the calibration films was in the same order of the exposure to be tested in experimental arrangements. Two Victoreen ionization chambers were placed with their centers 10 and 15 cm. respectively from the center of the source. With the readings of chambers and the inverse square law, it was then possible to calculate dosage in gamma roentgens at various distances from the center of the source. Such a curve was drawn on log-log paper. Because of the fact that the calibration source was not a point, the curve had to be adjusted to a 1.5 cm. tube from published tables[11] which made a noticeable difference only at the shorter ranges. The correlation of the darkening of the film to gamma roentgens was then possible. From these data the characteristic darkening curve (Fig. 1) was constructed to read gamma roentgens from density of the film on a semi-log scale.

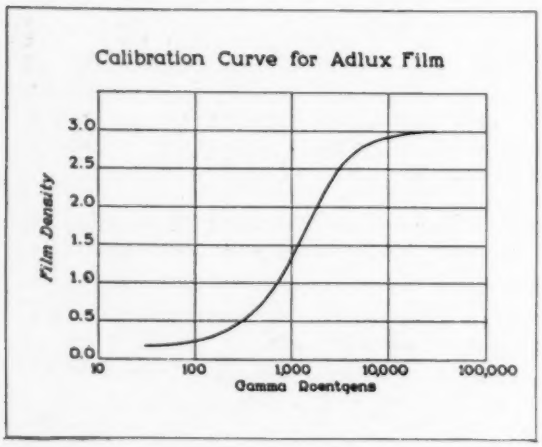


FIG. 1. Characteristic darkening curve for film used in experiments.

After development of the experimental films they were marked in grid lines with pencil 1 cm. apart. Readings were taken at the intersections of the lines and transferred to scale diagrams on graph paper. Additional readings were taken at closer points where necessary. From these plots specific isodoses in gamma roentgens could be drawn using the calibration curve. The results of the experiments are shown in Figures 2 to 7. The isodose lines shown are for 4,000, 1,000, and 500 gamma roentgens. They are represented because they include the straight portion of the calibration curve in the range tested.

RESULTS

The diagrams presented reveal the contours of the radiation pattern around the radium implantations for comparison. These diagrams were prepared for a normal sized uterus in standard relationships to the other pelvic organs.[11] The variations seen are due mainly to the spatial distribution of the radium sources only, since the exposure times, filters, and so forth, have all been reduced to the same equivalent. It can be seen that Plan I, which utilizes a short tandem alone, may be ineffective for treating a tumor which may lie in the fundus of the uterus. The substitution of a longer tandem, which extends from the external os to the top of the fundus as in Plan II, causes the field of radiation to be more elongated. The fields of radiation around the special applicator types, as in Plan III and Plan IV, conform more to the shape of the usual uterine cavity. The small cornual sources do produce areas where the radiation may be fairly intense, however. Also the median sagittal plane shows much narrower fields than the median coronal plane with these arrangements. Plan V shows how the multiple capsules cause the radiation field to conform to the shape of the cavity in which they are placed, but because their numbers are few and because they overlap one another, irregularities in the fields appear. These irregularities appear in the median coronal plane because

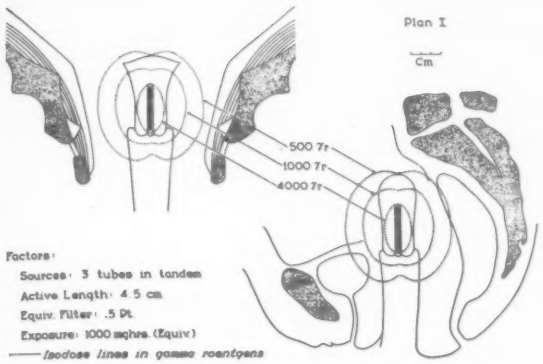


FIG. 2. Diagram of radiation distribution throughout standard pelvis for treatment Plan I.

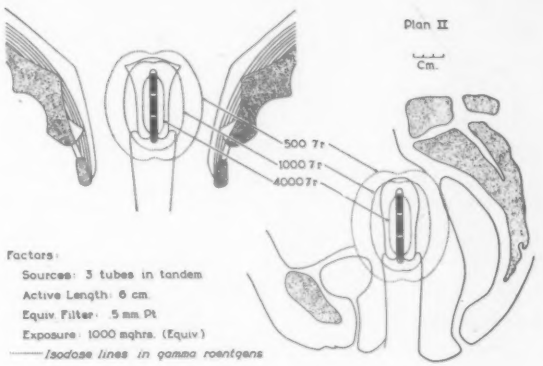


FIG. 3. Diagram of radiation distribution throughout standard pelvis for treatment Plan II.

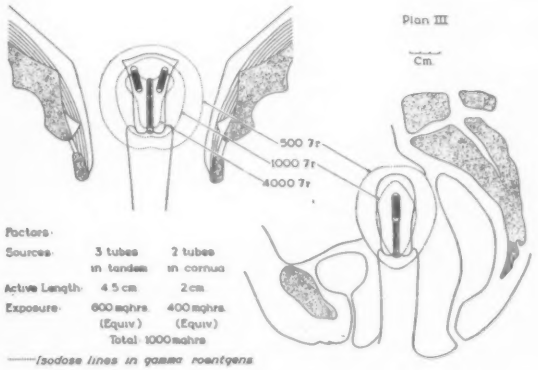


FIG. 4. Diagram of radiation distribution throughout standard pelvis for treatment Plan III.

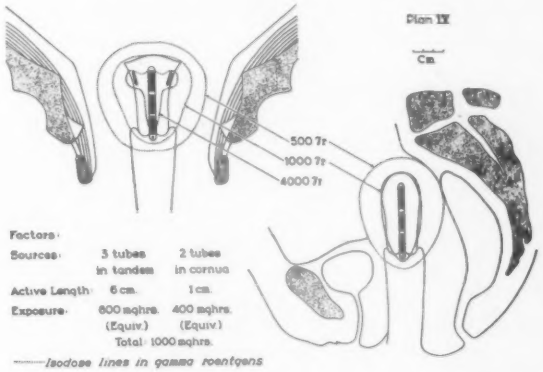


FIG. 5. Diagram of radiation distribution throughout standard pelvis for treatment Plan IV.

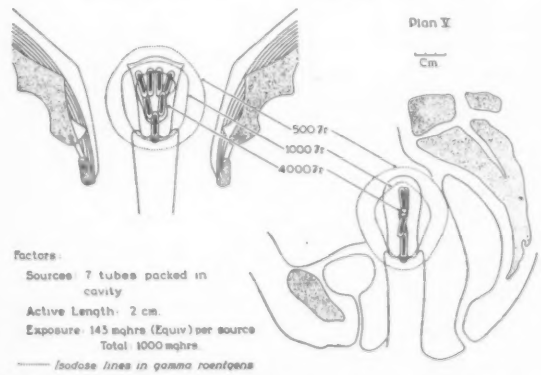


FIG. 6. Diagram of radiation distribution throughout standard pelvis for treatment Plan V.

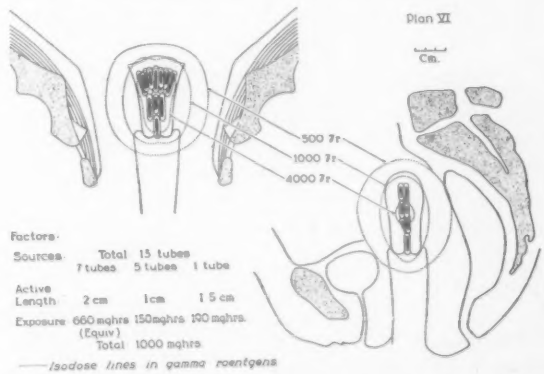

Plan VI
Cm.
500 7r
1000 7r
4000 7r
Factors:
Sources: Total 13 tubes, 7 tubes, 5 tubes, 1 tube
Active Length: 2 cm., 1 cm., 1.5 cm.
Exposure: 660 mghrs., 150 mghrs., 190 mghrs. (Equiv.)
Total: 1000 mghrs.
Isodose lines in gamma roentgens

FIG. 7. Diagram of radiation distribution throughout standard pelvis for treatment Plan VI.

overlapping removes the ends of some of the sources from the surface of film. In Plan VI in which more and smaller sources are used, the irregularities become smoothed out; there are essentially two layers of sources in this set-up. In actual practice the endometrial cavity is essentially a potential space that can be made deeper in the anteroposterior direction by packing. The radiation fields for this plan appear to conform to the shape of the uterus better than any of the others.

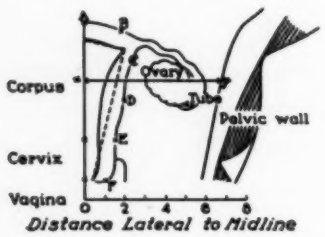
One attribute of a theoretically desirable radium application plan is homogeneity of

the radiation fields. This characteristic is difficult to measure or express numerically. However, a method of comparing the uniformity of the implantation schemes studied in relation to the uterus is presented in Table I. Certain points around the surface of the uterus were taken from a standard diagram[11] and designated as point *A*, *B*, *C*, and so forth, in the figure. The values for the radiation doses falling at these points expressed in gamma roentgens for 1,000 mg-hr. exposure are tabulated for each plan in Table I. The greater the uniformity, the more nearly alike the values should be at these points. Thus, the difference between the minimum and maximum doses should be less with more uniform radiation. Table I shows that the uniformity increases with the addition of more and more sources of radiation as progression is made from Plan I to Plan VI. Also, the fact that the minimum dose in all planes lies near the fundus of the uterus, and that the maximum dose usually falls near the internal os is brought out. Plan IV is somewhat unusual because of the small, strong, cornual source. Here the maximum dose is in the region of the horn, but the difference between minimum and maximum dose is great and provides, therefore, a field of radiation which lacks in uniformity.

Table II has been prepared to show the effect of this uniformity on milligram-hour exposure. The attribute of homogeneity in radiation fields from a radium implantation plan becomes manifest in the minimum and maximum doses. The minimum dose should be high enough to be lethal to all tumor cells, while the maximum dose should be below that which will cause complete cel-

TABLE I

TABLE SHOWING VALUES FOR RADIATIONS FALLING AT SPECIFIC POINTS AROUND THE SURFACE OF THE UTERUS IN GAMMA ROENTGENS PER 1,000 MG-HR. EXPOSURE FOR THE TREATMENT PLANS STUDIED



VARIATION IN UNIFORMITY OF RADIATION DISTRIBUTION AROUND UTERUS WITH SEVERAL TREATMENT PLANS

Description of Treatment Plans				Dose in Gamma Roentgens at Indicated Points						
#	Type	Sources	Exposure	A 7r	B 7r	C 7r	D 7r	E 7r	F 7r	(Max.-Min.) 7r
I	Tandem	3 small	1000 mghrs.	450 −	600	900	2400	3200 +	2300	2750
II	Tandem	3 large	1000 mghrs.	610 −	610 −	1000	2100	3000 +	3000 +	2390
III	"Y" Applicator	3 small 2 large	1000 mghrs.	700	630 −	2000	1650	2700 +	1700	2170
IV	Hysterostat	3 large 2 small	1000 mghrs.	1000 −	1200	4000 +	2400	2000	1700	3000
V	Multiple Capsules	7 large	1000 mghrs.	900 −	900 −	2050	2400 +	2400 +	1100	1500
VI	Multiple Capsules	13 small	1000 mghrs.	1100	1100 −	2400	2400	2600 +	1900	1500

− Minimum Dose + Maximum Dose

lular death to all tissues.[11] If we should arbitrarily consider 7,000 gamma roentgens as the dose necessary to cause death of the cancer cells without permanent injury to the normal tissues, we can express the factor K in the second column of the table as 7,000/min. dose. Then, it would be necessary to multiply the exposure time 1,000 mg-hr. by this factor to achieve 7,000 gamma roentgens at the point of lowest dosage. Of course, if this is done, the maximum dose must also be multiplied by the same factor, and the resultant dose as the point of maximum intensity is given in the third column. Table II shows that as the number of sources increases, the factor K decreases. With this decrease the resultant dose at the point of maximum intensity becomes less. If we should again arbitrarily decide that doses above 1,500 gamma roentgens may cause general tissue necrosis and deleterious effects, we find that only the resultant doses for Plan V and Plan IV decrease toward 1,500 gamma roentgens.

Conversely, if we should take the value at the point of maximum dosage for each plan and express the factor necessary to bring this dose to 15,000 gamma roentgens as K^1 in the table, we find that there is an increase in this factor with an increase in the number of sources used. With this increase we find that the value of the minimum dose may be raised and it is only with the treatment Plans V and VI that the minimum dose approaches 7,000 gamma roentgens.

The uniformity of each plan can then be expressed in the table as the difference between factor K and factor K^1, because the less this difference, the greater the uni-

TABLE II

TABLE SHOWING HOW MINIMUM AND MAXIMUM DOSAGE VALUES MAY AFFECT THE RANGE OF PERMISSIBLE MILLIGRAM-HOUR EXPOSURE FOR EACH TREATMENT PLAN STUDIED.

Effect of Minimum and Maximum Doses on Possible Total Exposures

Treatment Plan		Dose at Lowest Point (Min.)	Factor Necessary to Raise Min. to 7000 γr	Resultant Dose at Highest Point (K × Max.)	Dose at Highest Point (Max.)	Factor Necessary to Bring Highest to 15,000 γr	Resultant Dose at Lowest Point	Difference Between Factors
#	Description	γr	$K=\frac{7000}{\text{Min.}}$	γr	γr	$K^1=\frac{15000}{\text{Max.}}$	K' × min.	(K - K')
I	Small Tandem	450	15	46,000	3200	4.7	2115	10.3
II	Large Tandem	610	11.3	24,700	3000	5	3050	6
III	"Y" Applicator	630	11	29,700	2700	5.5	3465	5.5
IV	Hysterostat	1000	7	28,000	4000	3.8	3800	3.2
V	Multiple Capsules	900	7.7	18,480	2400	5.7	5130	2
VI	Multiple Capsules	1100	6.3	16,380	2600	6	6600	0.3

formity. Table II shows that only with Plan V and VI does this difference approach unity. Thus, with a more uniform field of radiation a greater milligram-hour exposure can be given with less danger of overdosage to points in the uterine wall and still achieve a more effective level of dosage throughout the area. However, experience has shown that there will be some undesirable necrosis in the proximal portion of the uterine musculature with high dosages, so

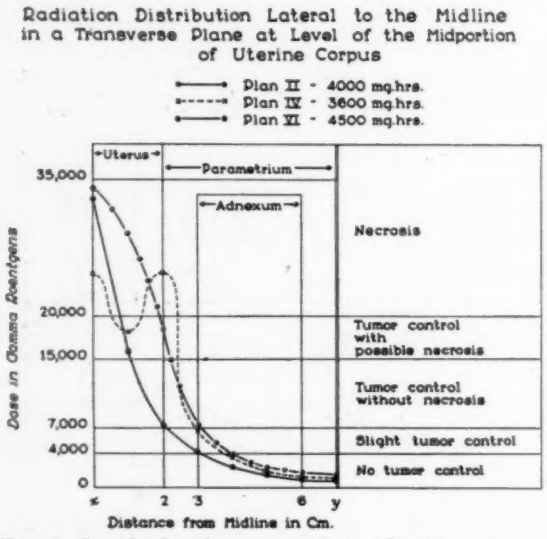


FIG. 8. Graph showing comparison of various treatment plans on the basis of the effective doses falling on the parametrium. Milligram-hour exposures in the range of the highest practical levels.

exposures in the order of 6,000 mg-hr. are not usually used in practical application.

In addition to speculation on the possible effect of radiations falling in the region of the uterine wall, the range of the radiations emitted from these implantations in relation to the parametria and adnexa is interesting to explore. In most instances, to ascertain clinically whether early extensions lie beyond the confines of the uterus or whether there may be small ovarian metastases is impossible. Doses in an effective range delivered beyond the uterus without causing dangerous necrosis are advantageous. Figure 8 has been prepared to demonstrate the experimental results with this in mind. The graph plots the radiation at various points lateral to the mid-line of the uterus in a transverse plane through the mid-portion of the uterine corpus. For reference this axis is shown as line *x–y* in the standard diagram shown in Table I. The ordinate gives distance in centimeters from the mid-line along the axis *x–y* and the abscissa shows doses in gamma roentgens. The space occupied by the uterus, the proximal parametrium, the adnexum, and the pelvic wall are indicated. The doses which may be deleterious because of necrosis, those which will be ineffective and those which will be effective without necrosis, are also indicated. Three treatment plans are plotted at the milligram-hour exposures at which they are usually given.[3,10,15] Plan II at 3,000 mg-hr. shows a rapid exponential fall in dosage level lateral to the mid-line, so that effective levels do not appear in the parametrium. Plan IV at 4,000 mg-hr. shows the higher dosage ranges maintained lateral to the uterus, but they fall rapidly and they may even be too high in the proximal parametrium. In Plan VI at 5,000 mg-hr. the dosage level is quite high in the region of the uterus itself, and there is again a rapid fall to ineffective levels before the adnexum is reached; but the proximal parametrium would seem to be effectively irradiated. In none of these cases does the pelvic wall receive doses at therapeutic levels.

DISCUSSION

The limitations of these experiments and the interpretation of their results given above need emphasis. The manifold problems of endometrial cancer cannot be oversimplified and answered by the results of such experiments as this. The purpose of this work was to study but one phase of the clinical problem; therefore, it was necessary to eliminate many of the important variables. As mentioned, variation in the size and shape of endometrial cavities were not taken into account. The plans studied were limited by the radium supply available. The arrangements of sources were rigid and the possibility of change in their conformation was excluded.

The results of the experimental method have been compared to those from calculations or measurements published by others in comparable instances.[6,7,8,12] Figure 9 shows the radiations measured lateral to the mid-line of the tandem used in Plan I compared with calculations for a similar source at this point. Here the calculated values are somewhat higher than the measured ones at the closer distances and slightly lower farther away. The effect of scattering and absorption in the phantom was not accounted for within the first 3 cm. All in all, the curves are reasonably similar.

Likewise, an attempt was made to correlate the measured values for the multiple capsule method demonstrated in Plan VI with those published by Heyman and Benner [7,8] for similar arrangements. Benner performed experimental measurements around the various sized "irradiators" used by Heyman in his packing technique. The measurements were made by suspending bags filled with these "irradiators" in air. Around each bag he attached a string of ionization chambers 1 cm. in diameter. These were centered 1.5 cm. from the surface of the bag. Average readings were taken in two planes and these were used to determine the necessary exposure time for various sized groups of sources as compared to an empiric method of Heyman. Measurements in these planes were expressed as Imc.

If we should take his values and attempt to translate them into gamma roentgens for comparison with the experimental method used, we would obtain the following:

Sources: 13
Strength: 8 mg. each—104 mg. total
Average readings: 7.75 Imc.
Exposure: 16.25 hr.—1,690 mg–hr.
7.75 Imc. × 8.5 r_γ/hr. = 65.87 r_γ/hr.
65.87 r_γ/hr. × 16.25 hr. = 1,070.4 r_γ or 633 r_γ/1,000 mg–hr.

Readings from the films for Plan VI were:
Source: 13
Strength: 11 mg. each or 140 mg. total
Exposure: 7.6 hr. = 1,000 mg–hr.

Average readings in two planes along the same surface as above were:
700 r_γ/1,000 mg–hr.

These calculations check remarkably well, but are subject to some error because of the difference in the experimental methods and the necessity of transposing the data for comparison.

To compare the results on the basis of expected biological reaction is natural as far as the interpretation of the results is concerned. If interpretations are made from radiation data alone, it is necessary to suppose arbitrary radiation levels. This ignores variation in radiosensitivity of the tumor cells; the characteristics of the tumor bed; the amount of infection present; and the intensity factor of the radiations. The radiation levels used here are somewhat standard[11] and at least the results are comparable among the treatment plans studied.

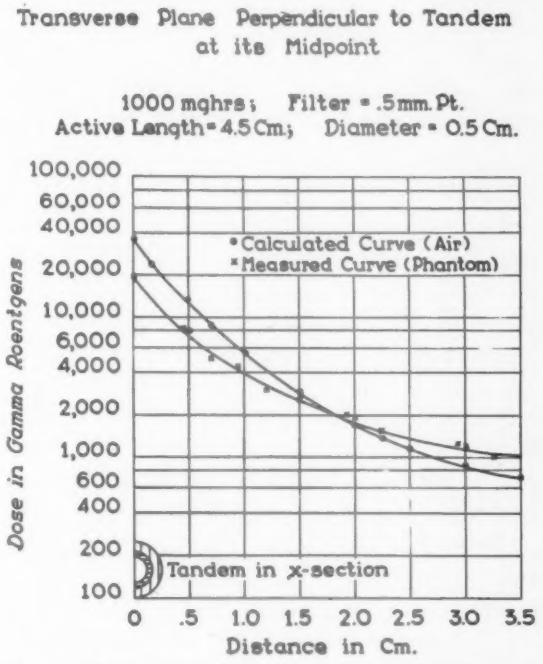


FIG. 9. Comparison between calculated and measured values for radiation distribution lateral to mid-point of tandem as described in Plan I.

With these limitations in mind, one can then evaluate the results more precisely. the experiments do show that the field of radiation for intrauterine radium implantation can be made more effective by adding as many sources as possible. The effectiveness increases because of increased uni-

formity of the fields, which allows greater milligram-hour exposures with more safety. One can expect that this improvement in radiation treatment will be translated into better clinical results.

Most reports on the microscopic evidence of residual tumor in uteri removed after intrauterine radium show the presence of recognizable cancer cells in about 50 per cent of the cases.[2,14,15] Technical improvement in the radium treatment showed more effective eradication of endometrial cancer in an earlier report by one of us.[10] A more intensive study of removed uteri by Stowe[14] showed a similar decrease in incidence of residual tumor with improvement in radiation technique. Such improvements may result in better survival rates for patients upon whom operation is not performed. Heyman and Benner[8] have shown a remarkable increase in survival rate that may be attributed to improvement of treatment technique.

The value of preoperative radiation treatment in operable patients is still unproved in the minds of many surgeons. Taylor and Becker[15] state that no significant conclusion on this point could be drawn from their recent series. However, they reported presence of residual cancer in about 49.6 per cent of the uteri removed after intrauterine radium treatment by a tandem. Of these, the survival rates for those showing residual tumor was of the order of 44 per cent and those not showing residual tumor about 74 per cent. A preliminary, and as yet unreported, study of the results from the Barnard Free Skin and Cancer Hospital and Barnes Hospital shows a greater survival rate in those patients treated by radiation and hysterectomy whose uteri show no evidence of residual carcinoma.[1] Such results as these may be due to the fact that the tumors are not extensive if they can be eradicated by preoperative irradiation, but the tendency to see less residual cancer after multiple radium capsule applications and the better survival rate when cancer is absent at the time of hysterectomy makes one feel that the improvement in technique is valuable even as a preoperative measure.

SUMMARY

1. The radiation distribution around six schemes of intrauterine radium application was explored by means of a film method of dosimetry.

2. From these studies the uniformity of the radiation fields for each of the plans was studied and comparisons were made. It was found that the characteristic of uniformity increases measurably with an increase in the number of sources used. This fact was correlated with expected biological results on the basis of tissue doses alone. It was found that implantations utilizing multiple radium capsules in a packing technique gave a better experimental result than any of the other types tested.

3. The parametrial doses from three types of implantations at the milligram-hour exposures usually used in therapy were compared. It was found that the multiple capsule method gave a wider field of radiation than the others, but that none of the methods delivered appreciable amounts of energy to the regions occupied by the adnexa.

4. Improvement in radium implantation techniques which yield improvement in the uniformity and amount of radiation delivered to the uterus should reflect itself in better clinical results.

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CANCER OF THE CORPUS UTERI FOLLOWING RADIATION THERAPY FOR BENIGN UTERINE LESIONS*

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THIS study is concerned with the part that previous irradiation for benign uterine lesions may play in the etiology of cancer of the corpus uteri. In the following study, the terms "cancer of the corpus uteri," "cancer of the fundus," and "cancer of the endometrium" are used interchangeably as applying to the same pathological entity.

ETIOLOGY OF CANCER OF THE CORPUS UTERI

Many authors have mentioned the probable etiologic factors in the production of malignant tumors, irrespective of their site of origin, or of tissues involved, such as age grouping, chronic irritation, heredity, repeated physiologic reparative processes, hormonal, chemical and physical agents. Infertility, nulliparity, and overweight have been added to the list in cancer of the corpus. In a recent paper based on many of the same patients used in this study, Taylor and Becker[12] have reported an average age of 57.4 years in a series of 368 previously untreated patients with cancer of the endometrium. In their series, the onset of symptoms due to cancer was postmenopausal in 73.86 per cent of the patients; 31.5 per cent were nulliparous. Certainly cancer of the endometrium arises from a site of periodic reparative processes over the course of many years, coincidental with the menstrual cycle. Recurrent proliferation and repair of the endometrium normally remain within certain limits under control of ovarian hormones. The possibility that cancer is merely a continuation or progression of originally normal proliferation of the endometrium has often been mentioned. Taylor[11] has described the etiologic and clinical points of similarity in endometrial hyperplasia and cancer of the endometrium. Randall[7] has stated that the woman noting postmenopausal bleeding who is not experiencing hot flashes and who does not show vulval or vaginal changes attributable to estrogen lack is very likely bleeding from cancer of the endometrium. The endometrial hyperplasia, approaching adenoma malignum of the corpus, associated with the estrogen producing granulosal cell tumors of the ovary, is further evidence of endocrine etiology in cancer of the endometrium. The converse observation of theca cell activity (and presumably hyperestrinism) in endometrial cancers has been reported by Smith[10] who found theca cell activity in 180 patients suffering with cancer of the corpus, and studied after radical pelvic surgery.

POST-IRRADIATION ASPECTS

Skin cancers and bone sarcomas are occasional but well recognized sequelae of exposure to such physical agents as sun rays, roentgen rays, and radium. Whether cancer of the endometrium may occur as a result of therapeutic irradiation is a frequently raised and moot question. Corscaden[3] writes that the likelihood of a cancer growing in the uterus is believed by many to be increased by the irritating effects of a therapeutic dose of radium, and by others to be diminished by the same factors. He concludes from observation on a series of 393 patients followed from one to seventeen years that the use of radium and roentgen rays for the treatment of benign uterine lesions is relatively harmless. In a later contribution, Corscaden and Gusburg,[4] in following for 6.7 years 1,100 women who had received a radium thera-

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peutic menopause for benign causes of bleeding, found 15 patients with carcinoma of the uterus; 9 located in the corpus (0.81 per cent, or 1–122); 6 in the cervix. He concludes that the number in the cervix being what they should be, those in the corpus were three times the number to be expected in the general population. He failed to say how he arrived at the number to be expected from the general population. Koff, in discussing a paper by Schmitz and Towne,[9] quotes Corscaden as saying that, "On a statistical basis, 9.6 per cent of women 30 to 55 years of age requiring treatment for excessive uterine bleeding will sooner or later develop carcinoma of the uterus. In comparison to women of the same age group in the general population, the incidence of carcinoma of the uterus is approximately one-third as great." We have been unable to learn the prevalence in the general population. Scheffey[8] calls attention to the occasional reports of uterine cancer following irradiation for benign lesions, and to 71 reported cases adds 20 of his own. He concludes from the analysis of these patients that there is no substantial evidence to show that radiation therapy either retarded or accelerated the development of cervical cancer, but that in 2 cases of cancer of the corpus uteri, because of a recent revision of pathological diagnoses, it seems as though the radium might have retarded, for six and thirteen years respectively, the progress of cancer of the corpus. In a recent paper, Crossen and Crossen[5] record the incidence of 4 cases of cancer of the endometrium in 526 cases of myoma of the uterus previously treated with irradiation, and compare the incidence favorably with 37 endometrial cancers subsequently found in 2,136 non-irradiated patients with myoma of the uterus.

ASYMPTOMATIC INTERVAL

Dermatologists, radiologists, and oncologists do see post-irradiation cancer, but it is well known that these cancers develop after an interval of years rather than weeks or months following the irradiation. Barrows[1] reported an operative case in which adenoma malignum had been present nine years previously when radium had been administered. Taylor, in discussing this report, mentions a patient known to have had an adenoma malignum of the uterus who survived for sixteen years without any treatment whatever, and at the end of that time presented little change in the histopathological appearance and characteristics of the tumor.

CRITERIA

It is appalling to note how many patients, especially in the non-specialized clinics, have been treated by roentgen rays or radium for "functional" or "menopausal" bleeding on the basis of history alone without endometrial biopsy. It is also astonishing to find the number of cases which have been considered benign without pathological substantiation at the time of the irradiation and who have been shown to have cancer of the endometrium a few months to a year later. Therefore, we have for this study chosen two criteria for cancer of the corpus uteri following irradiation for benign uterine lesions.

First: A negative endometrial biopsy preferably obtained with a curet, at the time of the irradiation for the benign lesion.

Second: An empirically selected time interval of ten years between the proved negative biopsy when the irradiation was administered for the benign lesion and the appearance of symptoms of cancer of the endometrium.

We are well aware that a small area of cancer may be missed by a curettage or by failure of a laboratory to examine all of the tissue submitted.

ANALYSIS OF MATERIAL

In this study the twenty-one year period from 1926 through 1946 was selected and the cases of cancer of the corpus uteri observed in Memorial Hospital during that period were reviewed. A total of 946 cases was found, in which pathological confirmation of the diagnosis was lacking in 141

TABLE I

CASES OF PROVED CANCER OF CORPUS UTERI IN WHICH PREVIOUS RADIATION THERAPY TO THE UTERUS HAD BEEN GIVEN

Case		Age	Parity	Biopsy of Benign Lesion	Treatment	Interval (years)	Pathology
*A.A.	1924–1934	70	0	Yes	Radium	10	Epidermoid and adenocarcinoma
B.B.	1943	65	3(6)	No	Radium	23	Adenocarcinoma, Grade 3
C.B.	1940	74	2	No	Radium	17	Adenocarcinoma, Grade 2
*M.B.	1924–1946	65	3	Yes	Radium	23	Adenocarcinoma, Grade 3
H.C.	1943	64	0	No	Radium	16	Epidermoid and adenocarcinoma
A.C.	1938	60	0	No	Roentgen ray	2	Adenocarcinoma, Grade 3
*E.D.	1920–1944	60	1	Yes	Radium	24	Adenoma malignum, Grade 2
E.D.	1940	71	0	Yes	Radium	3	Adenoma malignum, Grade 2
E.F.	1939	64	Not stated	No	Roentgen ray	10	Adenoma malignum
M.F.	1923–1936	71	1 Mis-carriage	No	Radium	13	Carcinoma
*M.G.	1928–1939	59	7	Yes	Radium	11	Adenocarcinoma, Grade 2
*R.G.	1928–1943	62	9	Yes	Radium	15	Adenocarcinoma, Grade 3
L.G.	1922–1933	57	2(4)	No	Radium	11	Adenocarcinoma, Grade 2
M.G.	1944	60	0	No	Roentgen ray	10	Adenoma malignum, Grade 2
B.G.	1943	57	3	No	Roentgen ray	5	Adenocarcinoma, Grade 3
M.H.	1938	68	9	No	Radium	19	Adenocarcinoma, Grade 3
H.H.	1940	50	Not stated	No	Roentgen ray	5	Glandular cancer
F.H.	1936	37	0	No	Roentgen ray	7	Adenocarcinoma, Grade 3
M.K.	1943	53	Not stated	No	Radium and Roentgen ray	18	Adenoma malignum, Grade 2
E.K.	1939	47	1	No	Radium	7	Adenocarcinoma, Grade 3
R.K.	1944	57	4	No	Roentgen ray	7	Adenocarcinoma, Grade 2
A.L.	1936	49	0	No	Roentgen ray	4	Adenocarcinoma, Grade 3
F.L.	1939	67	Not stated	No	Roentgen ray	4	Adenocarcinoma, Grade 3
A.L.	1934	68	3(6)	No	Roentgen ray	5	Adenocarcinoma
R.M.	1944	58	5	No	Radium	8	Adenoma malignum, Grade 2
A.M.	1945	70	0	No	Roentgen ray	10	Adenocanthoma, Grade 3
M.McC.	1942	51	0	No	Roentgen ray	10	Corpus carcinoma
D.M.	1928	54	2	No	Roentgen ray	18	Carcinoma
N.M.	1939	68	1	No	Radium	18	Adenocanthoma, Grade 3
*J.P.	1939–1945	43	3	Yes	Radium	16	Carcinoma
*S.R.	1942	68	1	Yes	Radium	18	Adenocarcinoma, Grade 3
B.R.	1933	62	3	No	Radium	8	Adenocarcinoma
H.S.	1930	53	3	No	Radium	8	Adenoma malignum, Grade 2
E.S.	1944	47	2	No	Roentgen ray	7	Adenocarcinoma, Grade 1
E.T.	1941	49	0	No	Radium and Roentgen ray	14	Glandular cancer
A.V.	1934–1943	44	2	Yes	Radium	8	Adenocarcinoma, Grade 3
*S.W.	1928–1939	56	0	Yes	Radium	10	Adenocarcinoma, Grade 3
H.W.	1928	42	1(2)	No	Radium	6	Adenocarcinoma
F.W.	1930–1940	39	1	No	Roentgen ray	10	Adenocarcinoma

* Proved negative biopsies when treated ten years before symptoms.

cases. The lack of pathological diagnosis in these 141 cases is believed to be due to several facts: Many cases have been referred here for radiation therapy following surgery and diagnosis elsewhere with unavailability of pathological slides for one reason or another. Other patients have had hysterectomy performed here after adequate radium therapy elsewhere, and examination of the specimen has failed to reveal residual tumor. Finally, rare cases have presented themselves in such a hopelessly advanced stage of the disease that no diagnostic or therapeutic procedure seemed warranted. There were, therefore, 805 cases of pathologically proved cancer of the corpus uteri. Thirty-nine of these cases were found to present a history of previous radiation therapy to the uterus exclusive of those cases which had, or are said to have had, radium or roentgen treatment for the cancer itself and had been referred to us merely for continuation of therapy. These 39 cases are briefly summarized in Table I.

It will be seen that of the 39 histopathologically established cases of cancer of the endometrium in which roentgen or radium therapy had been given previously for resumably benign conditions, only 24 presented intervals of freedom from symptoms for ten years or longer. Of these 39 cases, only 10 are known to have had pathologically proved benign uterine lesions at the time of their original radiation therapy. Thus, if only time is considered as a criterion, there would be 24 cases suitable for discussion, and, if a negative biopsy only is considered as a criterion, there would be 10 cases suitable for discussion. But, if both a negative biopsy and a ten year interval of apparent freedom from disease are considered as criteria, then there would be only 8 cases which present both qualifications, for 2 of these cases with negative biopsies show intervals of three and a half and eight years respectively, between administration of radium and onset of symptoms due to cancer. These figures are summarized in Table II.

It is proposed, therefore, that of the total of 805 cases of cancer of the endometrium observed in Memorial Hospital during the years 1926 through 1946, these 8 cases, if any, most likely represent post-irradiation cancers of the endometrium. These 8 cases present the following characteristics and are summarized in Table III.

Age: In these 8 patients at the time of diagnosis of cancer, ages ranged from fifty-five to seventy years, with an average age for the group of sixty-two years. All 8 patients were postmenopausal at the time of diagnosis of cancer. As near as could be told from a careful scrutiny of the charts, all 8 patients had undergone the menopause at the time of, and probably as a result of, their previous radiation therapy.

TABLE II

SUMMARY OF MATERIAL AVAILABLE FOR STUDY CANCER OF THE CORPUS UTERI, MEMORIAL HOSPITAL 1926–1946

Total number of cases	946
Number of pathologically proved cases	805
Number of cases previously irradiated	39
(a) with asymptomatic interval of 10 or more years	24
(b) with confirmed negative biopsies originally	10
(c) with both (a) and (b)	8

Parity: All of the 8 patients were married, but 2 of the group had never had children, the reasons for which were not stated. Of the remaining 6 cases, 2 were uniparous and the other 4 were multiparous, having had three or more children.

Interval: The time interval between administration of radium and the onset of symptoms due to cancer varied from the minimum interval of ten years to a maximum interval of twenty-three years.

Pathology: At the time of their original radiation therapy, the pathological report on the curettings of most of the 8 patients was "chronic endometritis." All but one of

the 8 patients had permanent sections filed. One had a diagnosis of "endometrium, menstrual type" made on the basis of a frozen section. All of the other 7 specimens were available for review. A recent review of these 7 slides in our Pathology Department has shown 1 case to have had cystic hyperplasia, and all the rest to have had lesions with intracavitary radium. One in addition had two external roentgen treatments, the exact dosage of which is not provided by the chart. The irradiation administered varied from 1,050 mc-hr. to 3,781 mc-hr.; this latter unusually large dose having been administered because of a clinical diagnosis of early cancer of the

TABLE III

CANCER OF THE CORPUS UTERI, MEMORIAL HOSPITAL 1926–1946

Cases Submitted as Post-Irradiation Cancers

	Case	Parity	Age	*Benign* Pathology	Treatment	Interval	Age	*Malignant* Pathology	Result
I	A.A. 1924 and 1934	None	60	Chronic endometritis (secretory endometrium)	Dilation and curettage and 2,438 mc-hr. radium	10	70	Adenocarcinoma Grade 3	Died July, 1939
II	M.B. 1924 and 1946	III	48	Chronic interstitial endometritis (secretory endometrium)	Dilation and curettage and 1,224 mc-hr. and 2 roentgen treatments	21	65	Papillary adenocarcinoma Grade 3	Died 10-16-46
III	F.D. 1920 and 1943	I	36	Cystic hyperplasia (cystic hyperplasia)	Dilation and curettage and 1,980 mc-hr.	23	60	Adenoma malignum Grade 2	Living and well 9-18-46
IV	M.G. 1928 and 1939	VII	48	Chronic endometritis (secretory endometrium)	Dilation and curettage and 1,050 mc-hr.	11	59	Papillary adenocarcinoma Grade 2	Died 3-19-40
V	R.G. 1928 and 1943	IX	47	Chronic endometritis (proliferative endometrium)	Dilation and curettage and 1,270 mc-hr.	15	62	Adenocarcinoma Grade 3	Died 5-11-44
VI	J.P. 1929 and 1945	III	43	Chronic endometritis (proliferative endometrium)	Dilation and curettage and 3,781 mc-hr.	16	59	Adenocarcinoma	Living with disease 5-22-46
VII	S.R. 1921 and 1942	I	47	Endometrium, menstrual type	Dilation and curettage and 1,200 mc-hr.	21	68	Adenocarcinoma Grade 3	Died 7-18-43
VIII	S.W. 1929 and 1939	None	45	Chronic endometritis (secretory endometrium)	Dilation and curettage and 1,080 mc-hr.	10	55	Adenocarcinoma Grade 3	Living and well 8-9-46

Eight cases of cancer of the corpus uteri believed to represent post-irradiation cancers. Under benign pathology the diagnosis in parentheses is that recently reported on review of slides.

essentially normal endometrium in various stages of the menstrual cycle. There was no evidence of cancer in any of the reviewed specimens.

The later specimens obtained from these 8 patients all showed adenocarcinoma of varying grades, 2 of which were classified as papillary adenocarcinoma. No significant variations from any other adenocarcinoma of the corpus uteri were noted in any of these 8 specimens.

Dosage of Radium: All 8 of these cases happened to be treated for their benign cervix which was not sustained histopathologically.

Results: Only 2 of the 8 patients are living and well at present, two and seven years respectively since their treatment for endometrial cancer. One patient is believed to be living with probable recurrent disease, and the remaining 5 patients have all died of recurrent, or persistent, cancer. Since this group of 8 patients is so small, it would be unwise to compare survivals with the accepted survival rate for cancer of the corpus uteri in an effort to determine

whether post-irradiation cancers of the endometrium are more aggressive than spontaneously occurring ones.

DISCUSSION

Of 805 patients with pathologically proved endometrial cancer, there were 8 (0.99 per cent) to whom radium had been administered ten years previously for pathologically proved benign uterine lesions.

Of the 8 patients, 7 received their original radiation therapy at Memorial Hospital in the years 1920 to 1929 (Case VII had originally been treated at another institution). During this decade, 1920 to 1929, a total of 1,244 patients with benign uterine lesions were admitted to Memorial Hospital; 752 were given radium therapy; 102 were given external roentgen therapy; and 390 were treated surgically or given no specific therapy whatever. Of the 752 patients treated with radium, at least 7 (0.93 per cent or 1–107) are known to have had endometrial cancer ten or more years later (Table IV). Without a 100 per cent follow-up on these 752 previously irradiated patients for ten or more years, it is impossible to state how many more did develop cancer of the endometrium.

TABLE IV

BENIGN UTERINE LESIONS, MEMORIAL HOSPITAL, 1920–1929

Total number of cases	1244
Number treated with radium	752
Number treated with roentgen radiation	102
Number treated surgically or given no specific therapy	390

While annual mortality rates of cancer of the uterus are available, statistics on the prevalence of endometrial cancer in the female population as a whole are not at present available. We are quite familiar with the Dorn statistics based on prevalence rates of cancer of the entire uterus per 100,000 *white* population[6] and with the excellent Connecticut Tumor Registry statistics[2] which give 147 per 100,000 *living* women over thirty years of age with carcinoma of the corpus in the years 1935 to 1946 or 1–680 population. Until, by reliable registration, we can obtain the yearly incidence of new cases over a period of years comparable to the years in which such a study as ours is undertaken, a true prevalence rate for comparison with our incidence cannot be known. Therefore it is impossible, at this time, to state whether irradiation for benign uterine lesions induces uterine cancer.

CASE REPORTS

These 8 cases, believed to represent post-irradiation cancers of the corpus uteri are abstracted below.

CASE I. A. A., a sixty year old diabetic nullipara, complaining of persistent regular menses, was found to have a symmetrically enlarged uterus three times normal size. On May 20, 1924, a dilation and currettage was performed and a fibroid tandem inserted for 2,438 mc-hr. The pathology report on the scrapings was "chronic endometritis." The patient was symptomatically improved and was lost to follow-up until August, 1934, when she returned complaining of vaginal bleeding of one month's duration. The uterus was found to be the size of a three and a half months' gestation with friable growth visible in the cervical canal. Biopsy of this was reported as "adenocarcinoma Grade 3." The patient was given intracavitary radium for 3,600 mc-hr. on August 14, 1934. Because of her age and diabetes, surgery was not recommended. She was given high voltage roentgen therapy, 700 r, through each of six pelvic fields and further intracavitary radium for 2,000 mc–hr. on December 3, 1935. Patient then remained fairly well until she developed a right hemoplegia in July, 1937. She died in July, 1939, probably with persistent cancer.

CASE II. M. B., a forty-three year old para III, complaining of menorrhagia and dysmenorrhea of six months' duration, was found to have a symmetrically enlarged uterus the size of a three and a half months' gestation. On November 25, 1924, a dilation and curettage was performed and a fibroid tandem inserted for 1,224 mc-hr. The pathological report on the scrapings was "marked interstitial endometritis." The patient was improved and discharged in January,

1929. She returned in May, 1946, complaining of urinary retention and bloody watery discharge, and was found to have a papillary friable growth protruding through the cervical os. This, on biopsy, was reported as "papillary adenocarcinoma Grade 3." The patient was given intracavitary radium of 3,600 mc-hr. on June 28, 1946, and after medical examination, was readmitted on September 13, 1946, for the purpose of hysterectomy. Her condition rapidly deteriorated with evidence of widespread dissemination of cancer, and she died on October 16, 1946, without benefit of further specific therapy. Autopsy permission was refused.

CASE III. E. D., a thirty-six year old para I complaining of irregular vaginal bleeding of fifteen months' duration was found to have a symmetrically enlarged uterus the size of a four months' gestation. On March 22, 1920, a dilation and curettage was performed and intracavitary radium for 1,040 mc–hr. administered. The pathological report was "glandular and cystic hyperplasia." Radium was again administered for 940 mc-hr. on December 13, 1921. The patient was improved and discharged on January 16, 1924. Because of vaginal spotting of two months' duration, she returned in August, 1944, after having a dilation and curettage and radium for 3,600 mc-hr. elsewhere. The pathology report was "adenoma malignum Grade 2." On August 29, 1944, a total hysterectomy and bilateral salpingo-oophorectomy was performed. No evidence of residual cancer was found in the specimen. Convalescence was uneventful and patient has remained without evidence of disease to the present.

CASE IV. M. G., a forty-eight year old para VII complaining of vaginal discharge, irregular menses, and intermenstrual bleeding of six months' duration, was found to have a heavy uterus one and a half times normal size. On December 11, 1928, a dilation and currettage was performed and a fibroid tandem for 1,050 mc-hr. inserted. The pathology report on the scrapings was "marked chronic endometritis." The patient was improved and was discharged on July 3, 1929. In December, 1939, the patient returned to Memorial Hospital because of constipation of nine months' duration and vaginal bleeding with lower abdominal pain of three months' duration. Examination revealed an irregular pelvic mass the size of a three and a half months' gestation with apparent metastatic deposits in the base of the bladder. Biopsy from the uterine canal showed papillary adenocarcinoma Grade 2. Because of the extent of the disease and because of the patient's marked debility, no specific therapy was offered. She was discharged to a nursing home where she died on March 19, 1940.

CASE V. R. G., a forty-seven year old para IX, complaining of vaginal bleeding of one year's duration, was found to have a uterus two and a half times normal size with a fibromyoma in the right horn. On August 28, 1928, a dilation and curettage was performed and a fibroid tandem inserted for 1,270 mc-hr. The pathology report on the scrapings was "chronic endometritis." The patient was improved and discharged on June 7, 1933. In July, 1943, the patient returned complaining of lower abdominal pain and vaginal bleeding of five days' duration. Examination revealed an irregular, non-tender lower abdominal mass extending to the umbilicus with evidence of vaginal implants. Biopsy from cervical canal and from the vaginal nodules showed adenocarcinoma Grade 3. The patient went elsewhere for treatment and allegedly received external high voltage roentgen therapy of 2,000 r to each of six pelvic fields, and 5,000 mg-hr. intracavitary radium. A panhysterectomy was performed elsewhere on December 9, 1943. The patient developed a rectovaginal fistula for which a colostomy was performed on April 29, 1944. The patient died allegedly with malignant disease on May 11, 1944.

CASE VI. J. P., a forty-three year old para III, complaining of general malaise, frequent menses, and lower abdominal pain of four months' duration, was found to have a somewhat heavy uterus with an irregular nodular cervix. With the presumptive diagnosis of cervical cancer she was given, on February 11, 1929, a cervical radium applicator for 2,946 mc-hr., and on the following day a dilation and curettage and insertion of a cervical tandem for 835 mc-hr. was performed. Pathological examination, however, showed only "chronic cervicitis and chronic endometritis." The patient remained well and was discharged on October 24, 1934. Because of vaginal spotting of two weeks' duration, the patient returned in April, 1945,

but went elsewhere for treatment and was allegedly given "44 hours" of radium in June, 1945. She returned to this clinic in December, 1945, at which time a papillary 2 by 1 cm. lesion on the right lateral vaginal wall was biopsied and reported as corpus carcinoma. On December 21, 1945, a dilation and curettage was performed and gold filtered radon seeds (6×0.83 mc.) were inserted into the vaginal lesion. A corpus applicator for 3,600 mc-hr. was given on December 29, 1945, and on February 14, 1946, total hysterectomy and bilateral salpingo-oophorectomy was performed. The patient developed vaginal recurrence and was given 2,000 r to each of four pelvic fields and 4,500 r through an intravaginal cone, both with 250 kv. technique. This patient was alive with disease on May 22, 1946.

Case VII. S. R., a sixty-eight year old para 1 was admitted to Memorial Hospital in May, 1942, complaining of irregular bloody discharge of three years' duration. Examination revealed the uterus to be irregular and enlarged to three times normal size. Past history disclosed that the patient had had a dilation and curettage performed at another hospital in New York City on February 14, 1921, and radium administered for 1,200 mc-hr. because of uterine fibroids. Curettings were reported as showing "endometrium, menstrual type." The menopause had ensued and the patient had then remained well until the onset of her present illness. On June 2, 1942, a dilation and curettage was performed with a pathological report of "adenocarcinoma Grade 3." The patient was given intracavitary radium only for a total of 4,560 mc-hr. Vaginal implants, which subsequently appeared, were treated with both interstitial and surface radium applications. The patient's general condition gradually deteriorated and she died elsewhere on July 18, 1943. Autopsy is reported as showing "adenocarcinoma of the corpus uteri with involvement of bladder, rectum, and peri-aortic nodes; and a coincidental colloid carcinoma of the gastric cardia as well."

Case VIII. S. W., a forty-five year old married nullipara, complaining of menorrhagia of two years' duration, was found to have a slightly enlarged uterus apparently caused by a fibromyoma. On January 15, 1929, a dilation and curettage was performed and a fibroid tandem for 1,080 mc-hr. inserted. Pathological examination of the scrapings showed "chronic endometritis." The patient was relieved of symptoms and discharged on July 23, 1930. Because of vaginal discharge and bloody spotting of one month's duration, she returned on May 16, 1939 and was found to have slight symmetrical enlargement of the uterus. On June 21, 1939, a dilation and curettage was performed and a corpus tandem for 3,600 mc-hr. inserted. Pathological examination of the scrapings showed "adenocarcinoma Grade 3." On October 7, 1939, total hysterectomy and bilateral salpingo-oophorectomy was performed. During the postoperative period the patient was given 750 r to each of four pelvic fields with 250 kv. technique. The patient has remained without evidence of disease since, and was well and asymptomatic when last heard from on August 9, 1946.

SUMMARY

A study has been made to determine what part, if any, irradiation of benign uterine lesions plays in the development of cancer of the endometrium.

A review of the opinions of recent authors has been presented as to: etiology of cancer of the endometrium, post-irradiation aspects, and asymptomatic intervals following the original irradiation.

Two criteria have been selected for the proved cases.

The material analyzed for the study consisted of:

(1) 946 patients with cancer of the endometrium during the years 1926–1946; thirty-nine of this group were said to have been previously irradiated, but only eight fulfilled both criteria.

(2) 1,244 patients treated with irradiation for proved benign lesions during the years 1920–1929 (752 by radium); seven of this group, after ten or more years, developed cancer of the endometrium.

The case histories of the eight cases believed to represent post-irradiation cancer of the endometrium are abstracted.

CONCLUSIONS

1. Of 752 patients treated with radium

for proved benign uterine lesions, at least seven (0.93 per cent or 1 in 107) developed cancer of the endometrium ten or more years later.

2. Since 100 per cent follow-up was not obtained, it cannot be determined that more patients did not develop endometrial cancer.

3. Until the prevalence of cancer of the endometrium in the female population as a whole is known, the comparative incidence of cancer of the endometrium in previously irradiated patients cannot be stated.

4. It is suggested that two criteria be accepted as evidence of cancer of the endometrium developing after irradiation for benign uterine lesions:

(a) Negative endometrial biopsy taken at the time of the application of radium for the benign lesion.

(b) An interval of ten or more years between the application of radium for the proved benign lesion and the appearance of symptoms of cancer of the endometrium.

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THE ROENTGEN CHANGES PRODUCED BY DIFFUSE TORULOSIS IN THE NEWBORN*

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CALCIFICATION of the brain is rarely observed on roentgenograms of the skull made during the neonatal period. The exact nature of the intracranial calcifications that were occasionally observed went without explanation until the recent work of Wolf, Dyke, *et al.*[6,20] demonstrated that visible intracerebral calcification was frequently associated with toxoplasmic encephalomyelitis, and it was thought that unexplained intracranial calcification observed in older children could well be due to residue of toxoplasmic granuloma that had undergone calcification during the prenatal and neonatal period.

Another cause for calcification in the brain in the neonatal period was demonstrated recently by Landing and Farber[9] who described the postmortem finding in an infant seven weeks of age of a diffuse-meningo-encephalitis caused by *Torula histolytica* (*Cryptococcus neoformans*). Their studies demonstrated, therefore, that the combination of degeneration of the brain, meningo-encephalitis, calcification within the brain, chorioretinitis and generalized visceral involvement found so characteristically in infants with toxoplasmic infection may be produced by another infectious agent.

Since the discovery of torulosis in that infant, the occurrence of that disease has been proved at postmortem examination on two more infants in the same laboratory.[7] In these two the diagnosis of torula meningo-encephalitis was suggested by the roentgenologist during life because of the similarity of the roentgen changes in the brain to those in the patient described by Landing and Farber.

This paper is concerned primarily with a description of the roentgenological changes in these 3 patients.

Torulosis or cryptococcosis is a relatively rare subacute or chronic infection caused by *Torula histolytica* (*Cryptococcus neoformans*), a fungus that is occasionally found on normal skin and in the feces and occasionally appears to inhabit the female genital tract, although it has been often thought that these cryptococci were not pathogenic. More than one hundred cases of torula meningo-encephalitis or diffuse torulosis have been reported,[18] but none of these patients have been under the age of three years and only 4 patients have been reported who were under the age of ten years.[1,5] Timerman[17] reported a fatal case of yeast meningitis occurring during pregnancy on whom a cesarean section was done. The delivered infant died two hours later, but showed no evidence of fungus infection at autopsy.

Torula may invade the lungs, skin, joints and subcutaneous tissues, but most frequently involves the central nervous system.[2,3,8,10] The exact mechanism of invasion is not certain in most of these patients, but it is thought to be by means of the respiratory tract, although evidently infection can occur by way of the middle ear, mastoid or paranasal sinuses.[11]

In our 3 patients because of the symptoms dating from birth and the apparent age of the lesions as observed on the examination of tissue removed at autopsy, the infection probably occurred either during the intrauterine life or at the time of delivery. It is thought that infection may have very well occurred in each instance

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during passage of the infant through the genital tract.

CASE REPORTS

CASE 1. M. T., a seven weeks old male, was admitted to the Infants' and Children's Hospital on March 6, 1945, because of failure to gain weight. The patient was born one month prematurely. The patient's mother had undergone a difficult pregnancy, experiencing frequent attacks of vertigo, anorexia which resulted in a 20 pound weight loss, and one episode of severe vaginal bleeding which occurred at the tenth week of her pregnancy. Abdominal pain was occasionally so severe that she was hospitalized for five days during the eighth month of her pregnancy, because of suspected

FIG. 1. Case 1. Lateral view of the skull shows enlargement of the calvarium suggesting mild hydrocephalus and extensive punctate and confluent calcification within the cranial vault.

FIG. 2. Case 1. The distribution of the intracranial calcification in the cortex and over the surface of the brain is shown in the posteroanterior projection.

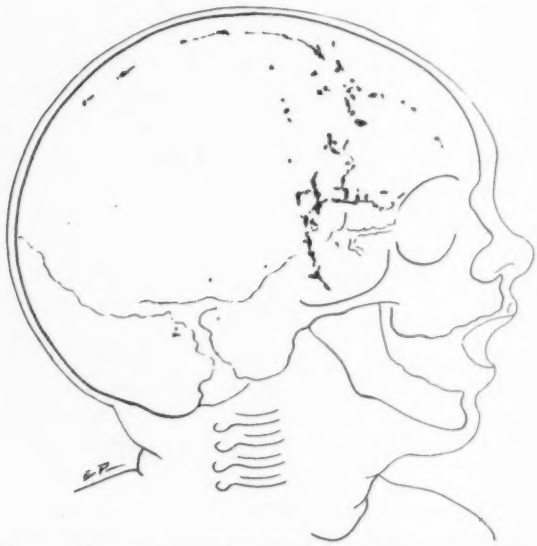

FIG. 3. Case 1. A drawing taken from Figure 1 shows the distribution of the intracranial calcification.

FIG. 4. Case 1. A drawing taken from Figure 2 shows that much of the calcification lies deep within the cerebral substance and that a considerable amount is in the cortex and meninges of the parasagittal region.

appendicitis. However, similar symptoms were evident during five previous pregnancies which resulted in apparently normal children. There was no history of rubella or other exanthems during the pregnancy. Labor lasted only one hour and delivery was precipitous. After birth the child developed cyanosis and was treated with oxygen. The day following birth there were twitchings and episodes of rigidity, which, however, diminished in frequency during succeeding weeks. Birth weight was 6 pounds, but the child failed to add weight in spite of gavage feedings.

A ventricular tap performed before admission to the hospital showed yellow fluid containing 189 red blood cells per cubic millimiter, 9 lymphocytes and a protein above 300 mg. per

Fig. 5. Case 1. The surface of the brain exposed at autopsy shows extensive cystic degeneration and multiple spots and plaques of calcification.

100 cc. Upon admission to this hospital the child weighed 6 pounds, 4 ounces and appeared emaciated and chronically ill. The head was slightly enlarged. The external auditory canals were very small and compressed so that the drums could not be seen. The eyeballs and palpebral fissure appeared normal. Cataracts were present bilaterally. The right eye showed chorioretinitis.

The spleen was palpable one and one-half fingerbreaths below the costal margin. Knee tendon reflexes were normal, but ankle clonus and Babinski sign were present bilaterally. The infant tended to maintain a position of opisthotonos. Following admission subdural taps were attempted and clear yellow fluid was thought to be derived from the subarachnoid space. The total protein of this fluid was 1,475

Fig. 6. Case 1. Photomicrograph prepared with von Kassa's stain shows extensive calcium deposition about degenerated cerebral tissue.

mg. The spinal fluid contained a total protein of over 1,400 mg. per cent and exhibited 27 monocytes per cubic centimeter on one occasion and 69 on another. The blood count showed 3,000,000 red blood cells, 55 per cent hemoglobin and 12,000 white cells with 12 per cent polymorphonuclear leukocytes, 60 per cent lymphocytes, 6 per cent monocytes, 20 per cent eosinophils and 2 per cent basophils. Urine and Hinton examinations were negative. The patient failed to gain weight and vomited frequently. No convulsive episodes were observed during the hospital stay, but the child was restless and generally irritable. After two weeks a purulent discharge developed from the conjunctiva and a culture showed *Staphylococcus aureus*. The patient died suddenly on the twenty-third hospital day.

Roentgen examination of the skull on admis-

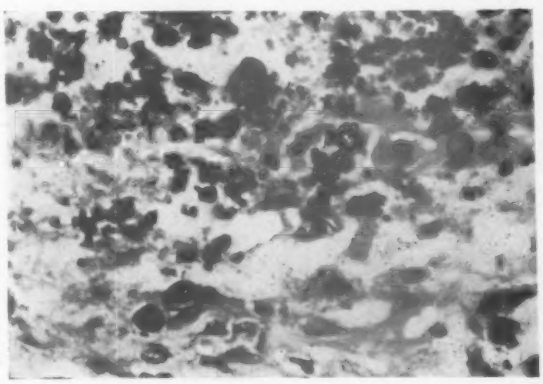

Fig. 7. Case 1. Photomicrograph of a portion of degenerated cerebral cortex shows numerous organisms, some of which are budding, morphologically identical with *Torula histolytica*.

FIG. 8. Case II. Lateral film of the skull shows slight enlargement of the head with prominent sutures. Faint punctate and confluent calcification is scattered throughout the brain.

sion showed that the calvarium appeared somewhat larger than normal, but the bone architecture showed no definite abnormality and the bones were moderately well calcified. There were numerous faint irregular shadows of calcific density in the frontal region, particularly on the right, and superficially along the parasagittal portion of the cerebral hemispheres. The calcification appeared punctate, although in some areas it tended to be confluent. Many of the shadows were curvilinear in distribution, suggesting that the calcification occurred about the margins of dilated ventricles or about the margins of areas of cystic degeneration of the brain. In spite of a negative skin test and negative blood neutralization test the diagnosis of toxoplasmic encephalitis was entertained.

Autopsy showed chronic inflammatory infiltration with many eosinophils in the lungs, pancreas, portal spaces of the liver, kidneys and testes. In addition, there was chronic epicarditis, perisplenitis, bilateral otitis media, bilateral microphthalmia with cataracts and purulent conjunctivitis and bilateral undescended testes. No organisms were discovered on bacteriological studies. Animal inoculation failed to produce any evidence of toxoplasmosis. The brain weighed 150 grams, which is a marked diminution from the normal of 500 grams. Chalky white plaques of varying sizes up to 1 cm. in diameter were scattered in the pia arachnoid, on the left side more than the right.

The majority of these were soft, but some felt hard and gritty. Microscopically the plaques were seen to contain granular calcium precipitate. The meninges throughout were heavily infiltrated by large and small mononuclears and eosinophils in granulomatous lesions. Many budding yeasts, morphologically characteristic of *Torula histolytica*, were found within the brain and meninges. The striking gross feature of the brain was displacement of the cerebral hemisphere by two large bilaterally symmetrical bulging cysts, each of which was found to contain about 100 cc. of clear yellowish brown fluid. The walls of the cysts were thin and transparent, so that it was possible to see through them the outlines of markedly dilated lateral and third ventricles. Sections of the brain showed the cerebral tissue to be poorly demarcated in the cyst walls and it was largely confined to a parasagittal strip on either side of the midline and to the frontal and temporal areas. Microscopically the cortical tissues showed a diffuse astrocytic gliosis and apparent loss of all ganglion cells and calcium deposition in a narrow zone in the outer cortex and about the cyst-like lesions. The dilated lateral and third ventricles were filled with a cloudy fluid and their ependyma was covered with a thin layer of translucent mucoid material, smears from which showed a multiplicity of organisms re-

FIG. 9. Case II. In the posteroanterior projection the calcification appears to be in the meninges, in the cerebral cortex, and deep within the substance of the brain. The bones of the base of the skull appear to be of greater density than is usual at this age.

sembling *Torula histolytica*. The aqueduct was patent and the fourth ventricle appeared normal. The spinal cord showed marked edema, but no evidence of meningitis.

No yeast could be recovered from the granulomatous lesion in the lungs, nor from the peribronchial inflammatory reaction.

The mother of this patient has recently been delivered of another infant who appears normal in every way.

Case II. L. B. This male infant was admitted to the Children's Hospital at the age of nineteen days because of severe jaundice that had been present since birth. The patient was born nineteen days prematurely after an eight hour labor. The mother had exhibited no unusual signs or symptoms during her pregnancy and she had had no previous pregnancies. Although the patient was born in Pinehurst, North Carolina, the parents had been born and lived the major part of their lives in Massachusetts, and had gone to North Carolina for a short visit. The patient's father is of Italian ancestry, but the mother is of Greek extraction.

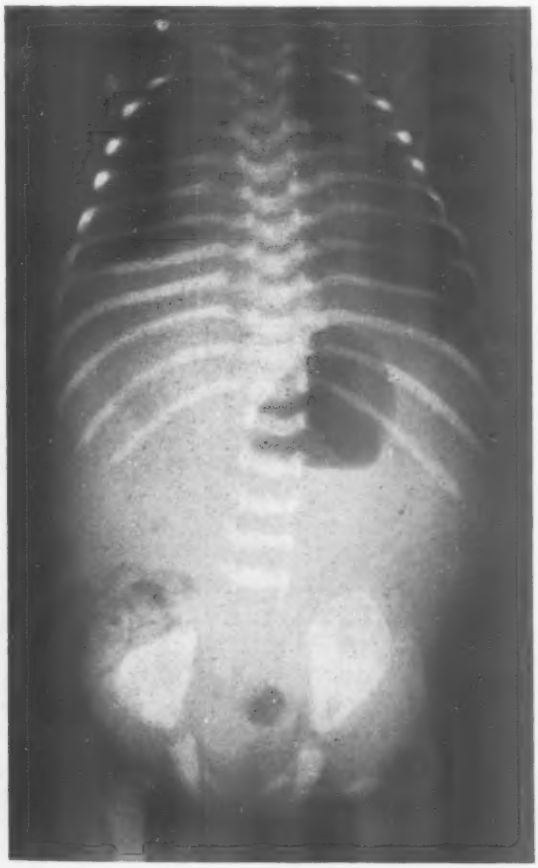

Fig. 10. Case II. A roentgenogram of the abdomen made in the erect position shows extraordinary enlargement of the spleen and marked enlargement of the liver. Calcification in the soft tissues cannot be found.

Fig. 11. Case II. Submetaphyseal decalcification, although prominent in this patient, is probably nonspecific and represents a growth disturbance even though organisms were recovered from the bone marrow.

The patient appeared perfectly normal at birth, except for jaundice which evidently became more intense during the first few weeks of life. At the age of one week abdominal distention was first noted, and that had evidently continued unchanged. The urine is said to have been dark and the stools are described as having been clay colored. Laboratory examination at the hospital in Pinehurst showed a high icteric index, acholic stools and bile in the urine.

On admission to the Children's Hospital the patient appeared poorly developed and somewhat undernourished and was deeply jaundiced. The sagittal suture appeared widely separated, but there was no other gross abnormality of the head. The heart and lungs showed no definite abnormality on physical examination. The

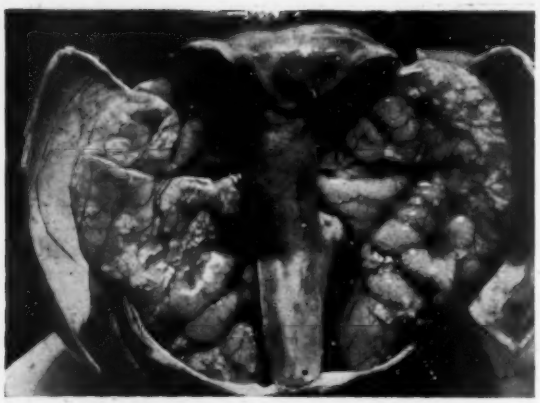

FIG. 12. Case II. The brain exposed at autopsy appears soft and flaccid due to dilatation of the ventricles and degeneration of tissue. Numerous flecks and plaques of calcification can be seen over the cortex.

abdomen was grossly distended and there appeared to be marked enlargement of both the spleen and liver.

During the stay in the hospital the patient developed loose, green stools and was given two transfusions and some intravenous fluid to combat dehydration. On two occasions during the hospital stay the temperature rose to 100° F. The child's condition deteriorated, his breathing became rapid and shallow with slowing of the pulse rate and he died on the fourth hospital day.

Laboratory examination showed no definite abnormality of the urine, except for a small amount of albumin and four plus bile. The red cell count was 2.95 million with 85 per cent hemoglobin. There was 12.8 thousand white cells with 47 per cent polymorphonuclear leukocytes, 40 per cent lymphocytes, and 2 per cent eosinophils. A second examination of the white cells showed that the count had risen to 22,600 with a considerable number of young forms. The blood bilirubin was markedly elevated with a total bilirubin of 39.2 mg. per 100 cc. Blood phosphorus and phosphatase were normal. The Hinton test was negative. The patient and both his parents were Rh positive.

Roentgen examination of the abdomen showed enlargement of the spleen and of the liver without evidence of calcification within either of these organs. A small amount of free fluid in the peritoneal cavity was suspected. Examination of the long bones showed no definite abnormality, except for well defined transverse zones of submetaphyseal rarefaction. In several of these zones there appeared to be actual loss of bony trabeculae.

Roentgenograms of the chest showed no definite abnormality of the heart or mediastinal shadows. The lungs were well aerated and appeared clear. No definite infiltration could be identified.

Examination of the skull showed that the bones of the base were relatively dense, but the bones of the vault were thin and poorly calcified. Scattered throughout the brain there was extensive confluent and punctate calcification, some of which evidently was overlying the cortex and a moderate amount of calcification was evidently within the cerebral substance itself, particularly on the left side. The skull appeared to be slightly enlarged, but a definite diagnosis of hydrocephalus could not be made.

Postmortem examination was carried out shortly after death and disclosed marked hydrocephalus and atrophy of the brain with numerous small granulomatous lesions similar to those observed in the first case. Within many of these granulomatous lesions there was deposition of calcium precipitate. The spleen was eight times larger than normal. The liver was moderately enlarged and showed a marked diffuse cirrhosis and moderate hepatitis. The kidneys were normal in size, but showed a diffuse interstitial infection with miliary abscesses. The bone marrow was hyper-

FIG. 13. Case II. The undersurface of the brain shows calcification scattered over the cerebellum and brain stem as well as over the cerebrum.

plastic and numerous organisms could be seen in the marrow. Organisms morphologically identical with *Torula histolytica* were observed in all of the organs with the exception of the lungs which exhibited only interstitial pneumonitis.

On culture the organisms grew out in grayish white colonies. Apparently identical organisms were grown from smears of the endocervix of the patient's mother.

Case III. Baby Boy S. This male infant was admitted to the Children's Hospital at the age of two and one-half weeks because of convulsions and almost continuous crying for the previous four days. The patient was born one month prematurely, a breech presentation after a short three hour easy labor. The birth weight was 6 pounds. The mother was well during her pregnancy, except for some morning sickness during the first trimester. The infant evidently was well at birth and returned home with the mother on the sixth day. The patient's parents are of Italian extraction. There is one four year old sibling, living and apparently well.

Two days before admission to the hospital the patient refused his feeding and began to cry continuously, drawing up his legs as if in pain and there were grasping and shaking movements of the upper extremities and clonic movements of the lower extremities.

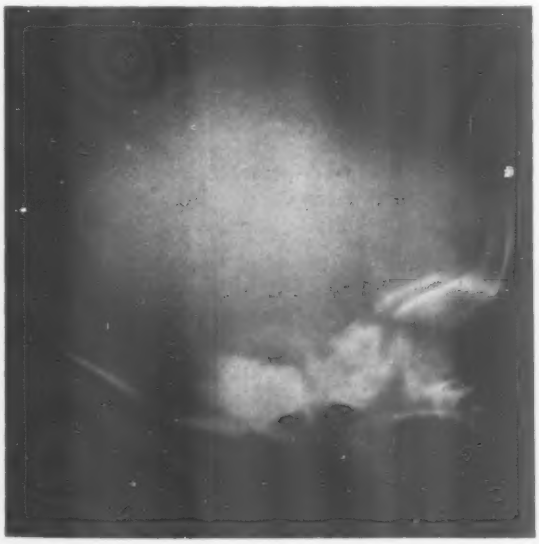

Fig. 14. Case III. The calcification over the surface of the brain and within the cerebral substance in this patient has a distribution similar to that in the preceding two patients.

Fig. 15. Case III. Interstitial pneumonitis, focal atelectasis and a large granulomatous lesion in the right upper lobe are prominent features in the anteroposterior film of the chest.

On physical examination the patient appeared irritable and hypertonic. Clonic motions of the extremities were frequent. No abnormality of the head was noted. The anterior fontanel was open, but was not bulging. The eyes appeared normal.

Examination of the heart and lungs showed nothing unusual except for a considerable increase in the rate of respirations. The abdomen was distended but soft, and a considerably enlarged liver and spleen could be felt.

Neurological examination showed only hyperactive reflexes.

Laboratory examination disclosed a red blood cell count of 3,000,000 with 13 grams, or 83.5 per cent, hemoglobin and 4,600 white blood cells and 66,000 platelets. The differential showed no definite abnormality, except for 4 per cent eosinophils and a moderate number of young forms. Many of the polymorphonuclear leukocytes showed toxic granules. Urine examination showed nothing unusual except for a considerable number of red cells during the last few days of the patient's stay in the hospital. On the ninth hospital day the patient had gross hematuria. The patient died on the tenth hospital day.

Roentgen examination of the abdomen showed marked enlargement of the spleen and liver which appeared homogeneous in density without areas of calcification.

Intravenous urogram showed prompt appearance of the dye bilaterally. The kidneys appeared normal in size, shape and position

FIG. 16. Case III. A film made after the intravenous injection of diodrast shows no gross abnormality of the kidneys or dye-filled bladder. There is extreme enlargement of the liver and of the spleen.

and no evident abnormality of either upper urinary tract or bladder could be detected.

Examination of the long bones showed no abnormality except for definite broad rather poorly defined transverse zones of diminished density in the submetaphyseal regions. No actual bone destruction or new bone formation could be identified. The soft tissues did not appear abnormal.

FIG. 17. Case III. The surface of the brain shows an appearance essentially similar to that shown in the preceding two cases.

Examination of the chest showed that the heart appeared to be essentially normal in size, shape and position. The mediastinal shadows showed nothing unusual. The lungs showed gross irregularity of aeration with bulging of many of the interspaces and some peripheral emphysema. There were numerous hazy rather poorly defined areas of increased density throughout each lung. The appearance suggested inflammatory reaction, although some superficial or lobular atelectasis in association with this was suspected.

Examination of the skull showed that the calvarium appeared to be definitely larger than normal. The sutures were prominent; the fontanelles were open, but not bulging. The

FIG. 18. Case III. The undersurface of the brain shows extensive calcification, degeneration of the brain, and cyst-like fluid collections in the leptomeninges.

bones of the vault were quite well calcified without evidence of bone erosion or destruction. There was considerable hazy, poorly defined and occasionally confluent calcification within the cranium. The distribution of this suggested calcification over the cortex and possibly within the brain substance.

Postmortem examination disclosed changes strikingly similar to those observed in the previous 2 cases. The brain showed marked hydrocephalus and atrophy with extensive calcification within granulomatous lesions, and numerous cryptococci were present both on smear and culture. The spleen was markedly en-

larged and numerous intracellular organisms could be seen. The liver was moderately enlarged with a slight diffuse cirrhosis and moderate hepatitis. The kidneys were slightly enenlarged with interstitial inflammatory reaction. The bone marrow was hyperplastic. The lungs showed considerable superficial and lobular atelectasis and in the right upper lobe there was a nodule, 1 cm. in diameter, that showed numerous organisms. Chorioretinitis and optic neuritis were present in both eyes.

DISCUSSION

It is interesting, although not necessarily significant, that these 3 male children were of Italian parentage. Each was born prematurely without definite illness of the mother during her pregnancy. The signs and symptoms presented by these 3 patients were so varied that a clinical diagnosis does not seem possible from the history alone. Two patients showed chorioretinitis, and 2 showed definite evidence of involvement of the central nervous system. The marked jaundice shown by one infant was not present in the other two. All 3 patients showed enlargement of the spleen and of the liver, and all evidently had slight enlargement of the head, although this was not noted on physical examination. Fever was not a feature in any of the 3 nor was the blood picture of value in establishing a diagnosis. Unfortunately, roentgen examination on these patients was carried out at so late a period in the course of the hospital stay that none of the laboratory examinations suggested by the roentgen findings could be carried out.

Roentgen examination in each instance showed a calvarium that appeared larger than normal, but with normal bone architecture, although the bones of the base seemed more dense than usual in one patient. Diffusely scattered throughout the brain there was in each instance diffuse punctate and confluent calcification and changes suggestive of enlargement of the ventricles. The extreme degree of hydrocephalus and degeneration could have been well shown by the appropriate air studies of the ventricular system. Roentgen examination of the long bones in 2 of the patients showed definite but probably nonspecific submetaphyseal rarefaction, although in 1 patient the appearance was suggestive of actual loss of bone trabeculae. The marked enlargement of the spleen and the enlargement of the liver were well visualized.

Although it is probably not possible to make an accurate roentgen diagnosis from these findings the demonstration of an enlarged calvarium with evidence of hydrocephalus and brain degeneration and loss of cerebral substance in association with an enlarged spleen and liver and with inflammatory or granulomatous lesions in the lungs should suggest the diagnosis, and the appropriate studies be carried out in an effort to isolate the fungus from the cerebrospinal fluid. It must not be considered that the submetaphyseal bone changes are indicative of anything more than faulty growth due to illness or the residual rarefaction so frequently seen in the premature infant, unless definite bone destruction can be seen.

DIFFERENTIAL DIAGNOSIS

The resemblance of the clinical features and roentgen picture of these patients to those with toxoplasmic encephalomyelitis is striking and it is probable that a definite etiological diagnosis cannot be made with any degree of certainty. However, extreme enlargement of the spleen is usually not associated with toxoplasmosis. It is very likely that many other organisms could produce similar roentgenographic and pathological changes. Certainly one would suspect that North American blastomycosis might produce a similar picture, although to date it has not been reported in the neonatal period.

Intracranial calcification following primary chronic coccidioidal meningitis has been reported[16] and it is quite likely that in areas where this infection is endemic similar changes may be observed in the newborn.

SUMMARY

Three patients with diffuse infection with the yeast *Cryptococcus neoformans* are presented.

Each of these patients showed evidence of mild hydrocephalus on roentgenographic study and diffuse punctate and confluent calcification of the severely degenerated brain. The calcification resembles that seen with toxoplasmic encephalitis.

Enlargement of the liver was present in each patient and enlargement of the spleen was striking.

Two patients showed inflammatory and granulomatous lesions in the lungs, and two showed nonspecific submetaphyseal decalcification of the long bones.

In each patient the infection was evidently acquired in utero, during delivery, or very early in the neonatal period. The damage produced by the fungus was severe and in these three patients fatal within a few weeks after birth.

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DISCUSSION

DR. JOHN CAFFEY, New York, N. Y. Dr. Neuhauser's findings show that torulosis as well as toxoplasmosis must be considered in the roentgen evaluation of intracerebral calcifications in the newborn infant. The identification of 3 cases of fetal torulosis in one hospital probably indicates that torulosis is not as rare as it is now believed to be and that it is being overlooked. It is also possible, as Dr. Neuhauser has suggested, that were more infant heads examined roentgenographically after inflammation of the central nervous system cerebral calcification would be found in some of these other types of encephalitis. This should be true in cerebral histoplasmosis, coccidioidomycosis, tuberculosis and blastomycosis. So far as I

know calcifications in the brain have not been identified in prenatal syphilis.

The presence of chorioretinitis in torulosis as well as in histoplasmosis makes the clinical differentiation of these two calcifying cerebral infections exceedingly difficult. The presence of splenomegaly, hepatomegaly and pulmonary inflammations in all of Dr. Neuhauser's patients with torulosis may serve to differentiate torulosis from histoplasmosis, because in the latter, changes in the spleen, liver and lungs are not so frequently found in the newborn.

It should be emphasized that microcephaly as well as hydrocephaly occurs commonly in toxoplasmosis; also malformations of the eye such as microphthalmia are seen in many cases of toxoplasmosis.

The findings of Dr. Neuhauser and his colleagues in these cases of neonatal torulosis constitute one more important addition to our knowledge in the rapidly expanding field of prenatal infections of the fetal central nervous system.

Dr. Neuhauser (closing). I would like to thank Dr. Caffey very much for his discussion. We, too, have seen quite a few patients who we thought had toxoplasmic encephalitis who exhibited microcephaly. We have seen the condition with calcification of the brain, of course. We have not had a chance as yet to see whether we can prove a diagnosis of torulosis without calcification. We have not seen enough patients.

In none of these 3 patients was the *Torula* recovered from the eye. I do not know how serious a search was made at the time. Actually, the examinations are not thoroughly complete and I will check on that, but to my knowledge, they were not recovered.

We have seen many older patients with calcification of the brain, both in childhood and adolescence, and particularly groups within families. We have 3 or 4 in a family which show widely distributed calcification. We have often thought that these changes were a residual of calcification within toxoplasmic granulomatous processes in the brain. We have no proof of that, so most of those go without specific etiological diagnosis.

TOXOPLASMOSIS

REPORT OF A CASE WITH ROENTGEN DEMONSTRATION OF UNUSUAL INTRACRANIAL CALCIFICATIONS

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AND

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TOXOPLASMOSIS is an entity of recent recognition. The protozoan *Toxoplasma* has been recognized only for the past decade and a half and the antemortem diagnosis of the infestation has been possible only for the past decade. Anyone interested in the history of this disease, its pathology, the development of the diagnostic studies and a review of the 26 proved cases reported in the literature is referred to the excellent articles by Callahan and his co-workers,[1] and by Pratt-Thomas and Cannon.[2]

Our case is reported because it presents the characteristic clinico-pathologic features of congenital toxoplasmosis with unusual intracranial calcifications.

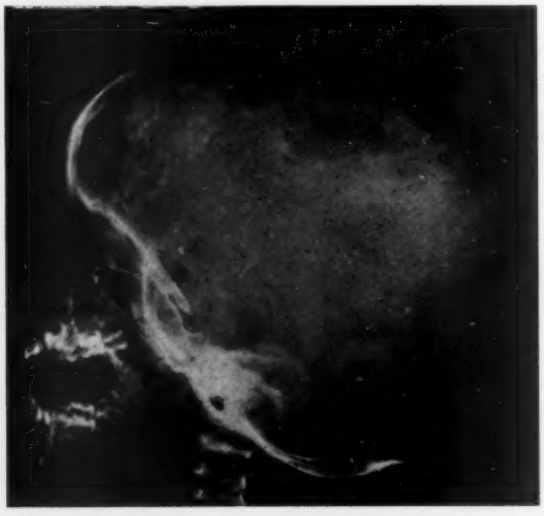

FIG. 1. This single right lateral plain roentgenogram of the skull shows the characteristic flaky calcification over the convex surfaces and at the base of the brain. The large size of the calvarium as compared to the facial bones is apparent and indicative of the extreme degree of hydrocephalus which Figures 2 and 3 show.

CASE REPORT

B. L. M., a white female child, born February 9, 1946, was admitted to the Greenville General Hospital in March, 1947, with the chief complaints of convulsions and blindness.

The child was born after seven months gestation by breech presentation and weighed 4½ pounds at birth. Shortly after birth the child had intermittent convulsions which subsided about two months later and did not recur until seven months of age. After recurring they persisted until the child's death. The convulsions became less severe with calcium medication and sedation, but generalized spastic contractions of virtually all muscle groups continued. At birth the child had convergent strabismus and never had more vision than merely light perception. It was only because of unusual nursing care that the child was able to survive at all.

At thirteen months of age the child was admitted to the hospital for diagnosis and definitive treatment. She presented a picture of hydrocephalus and constant muscular twitchings. She was thought to have bilateral cataracts on admission, and an internal strabismus of the right eye was seen.

Roentgen examination of the skull revealed a great deal of flaky calcification over the convex surface of the brain and at the base (Fig. 1). A tentative diagnosis of toxoplasmic encephalitis was made, and a ventriculogram showed severe internal hydrocephalus (Fig. 2 and 3).

During the ventriculographic procedure many calcified plaques were visualized on the surface of an extremely thin cerebral cortex. Several of these lesions were removed for biopsy. They

were examined by Dr. W. A. Derrick whose report is as follows:

"*Microscopic Description.* Two small pieces of tissue include (1) a bit of dura and (2) a bit of superficial cortex. The former is rather thick but shows no other change. The cerebral cortex reveals a superficial nodular calcification which is most striking. This probably includes the pia-arachnoid as well. It is accompanied by small numbers of surrounding lymphocytes, but one is not impressed with the inflammatory process. Tiny calcific, free and intracellular particles lie for some distance around the more solid nodular central portions, but no structures can be identified as living *Toxoplasma.*

"*Gross and Microscopic Diagnosis.* Mild chronic meningitis with marked superficial calcification of the cortex.

"*Note:* This is interpreted as being consistent with the healed stage of toxoplasmosis with secondary calcification."

Following ventriculography, specimens of the child's and the mother's serum were obtained and sent to Dr. Isaac Ruchman, Department of Bacteriology, University of Cincinnati. He carried out antibody neutralization studies on both sera and found both to have *Toxoplasma* antibodies.

Dr. J. W. McLean, ophthalmologist at the Greenville General Hospital, examined the child shortly after the initial roentgenograms were taken and reports as follows: "Through a dilated pupil I am unable to visualize the right fundus; however, fleeting glimpses of the left is possible. The left optic nerve is atrophic. There is one large area of quiescent chorioretinitis on the temporal side with marked pigmentation of the edges. The sclera, through this area, shines as a brilliant white surface. There are numerous floating vitreous opacities. On the nasal side of the left fundus is a large grayish membrane which resembles glial tissue. Examination of the mother's fundi shows nothing abnormal."

Examination of the urine was negative. The peripheral blood showed no abnormality and examination of the spinal fluid for abnormal cells, sugar and protein showed nothing abnormal.

Roentgen examination of the child's spine, chest and abdomen was normal. The mother's skull showed no evidence of calcification. There were no siblings. The child died in July, 1947. Postmortem examination was not obtained.

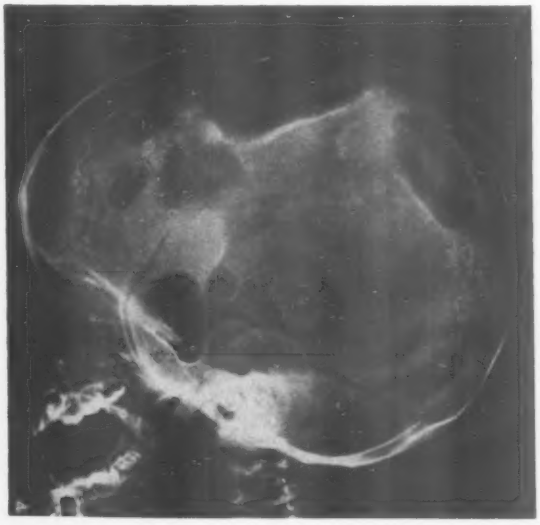

FIG. 2. This reproduction of a ventriculogram shows the extreme degree of internal hydrocephalus with air occupying practically the entire intracranial space. Calcification is again seen over the convex surfaces of the brain and in the region of the base.

FIG. 3. This anteroposterior projection shows the enormous size of the lateral ventricles and the extreme thinning if the skull as noted on the left where some of the air is seen in the subarachnoid region.

DISCUSSION

Callahan, Russell and Smith,[1] in reviewing the literature, find this disease to be widespread throughout the world, and this is the second case reported from the southeastern portion of the United States.[2] Since this child's disease was probably contracted from its mother, it is of note to mention something of the mother's background. She was born near Columbia, South Carolina, and lived there all of her life except for four years spent in Long Island and one year in Oakland, California. The only animals the parent had any contact with were a pet dog, during the last two months of her pregnancy, and a canary as a pet for one summer, two years before the child was born. Callahan reports that both of these animals are natural hosts of the *Toxoplasma.*

Callahan, Russell and Smith list some of the neurologic signs and symptoms in infantile toxoplamosis and our patient had all of them: internal hydrocephalus, muscular twitching, convulsions, spasticity, opisthotonos, retraction of head, stiff neck and paralysis.

Neuhauser and Tucker[3] state that the differential diagnostic possibilities of intracerebral calcifications of infectious origin should include the following: toxoplasmosis, torulosis, histoplasmosis, blastomycosis, and possibly malaria.

SUMMARY

We have presented the case of a white female infant who lived to be seventeen months old, and who showed the classical picture of congenital toxoplasmic encephalitis of convulsions, cerebral calcifications, chorioretinitis and hydrocephalus.

Antibody neutralization studies carried out on the child's and the mother's serum show both to have antibody reactions positive for *Toxoplasma.* Roentgenograms showing the unusual intracranial calcifications are presented.

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THE SKELETAL LESIONS IN LEUKEMIA

CLINICAL AND ROENTGENOGRAPHIC OBSERVATIONS IN 103 INFANTS AND CHILDREN, WITH A REVIEW OF THE LITERATURE*

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THE diagnosis of leukemia in infants and children is often made difficult by factors which do not operate significantly in adults. Chief among these are (1) the tendency of non-leukemic children to produce immature white blood cells in response to severe infections, and (2) the frequent absence of leukocytosis in children with leukemia. The demonstration of leukemic changes in the bones by roentgen examination provides valuable information for the detection of leukemia during early life. Numerous reports attest the value of roentgenologic investigation of the skeleton in leukemia. Kalayjian, Herbut and Erf[28] in 1946 found descriptions of 144 leukemic children who showed skeletal changes in roentgenograms; they added 2 cases. However, this relatively small group does not portray the true frequency of bone lesions, nor do single reports show the diagnostic limitations of roentgenologic examination. This report includes all cases of leukemia admitted to the Babies Hospital during the period from 1924 to 1947.

REVIEW OF THE LITERATURE

Descriptions of the skeletal lesions in leukemia are, for the most part, in case reports; the similarity of the lesions and of the associated clinical findings described independently by the individual authors is striking. It might seem unduly repetitious to review each report separately except for two facts: (1) there is no comprehensive survey available at present, and (2) the variations of the clinical pictures are not appreciated in a statement of the common features of the disease. This review includes the chief articles of historic interest, case reports of special interest, and review articles in an attempt to satisfy these deficiencies.

The first reports of skeletal lesions in leukemia antedated the discovery of the roentgen ray. Heschl[23] described a local osteolytic lesion in a leukemic patient in 1847, two years after the original description of leukemia by Virchow. In 1878, Neumann[39] reported 2 leukemic patients who had bone pain and multiple areas of bone destruction. Neumann reviewed some 20 case reports published since 1845; in several, mention was made of pain in the extremities, in some there were gross osseous lesions. Heuck[24] described diffuse leukemic osteosclerosis in 1879. He mentioned tenderness over the sternum in leukemia, a feature emphasized by Craver[11] forty-eight years later.

It is probable that some of the cases reported prior to Ehrlich's introduction of differential staining in 1891 would not meet current criteria for the diagnosis of leukemia, but there is no doubt that the general clinical features including skeletal lesions were well established by the time of Röntgen's discovery in 1895. These early observations were anatomical and they illustrate the value of careful skeletal examination at necropsy. The infrequency of such examinations at present limits our knowledge substantially.

Roentgen examination of a leukemic patient was reported for the first time by von Jaksch[26,27] in 1901. His patient was a twenty-four year old woman whose symptoms began in February, 1900, and whose course was described[26] up to December, 1900, because of the unusual roentgenographic findings. The patient died February 7, 1901, and the continuation record and autopsy protocol appeared in a second publication.[27] Typical signs and symptoms of leukemia were present; in addition the patient suffered from severe bone pain. Roentgenograms demonstrated osteosclerosis and periosteal new bone formation at the sites of bone pain. Reproductions of these early roentgenograms were surprisingly clear. Von Jaksch coined the term "periostitis multiplex cum myelocythemia" for

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what he considered to be a previously undescribed syndrome, the cardinal signs of which were periosteal proliferation, splenomegaly and myelocythemia. He believed the osseous changes were primary.

It is surprising that, despite the wider application of roentgenographic technique during the two decades which followed this report, there is a paucity of material on roentgen findings in leukemia. Pförringer[41] in 1913 and Oesterlin[40] in 1923 described roentgenographic changes in this disease. Pförringer's patient was a fifty year old woman with a tumor of the bone marrow leading to spontaneous fracture; her white blood cell count of 1,960,000 cells per cu. mm. is said to be the highest on record.[19] Oesterlin described roentgenographic findings "suggestive of syphilis or leukemia" in a two year old child with anemia, hemorrhagic tendencies and painful, swollen extremities. The leukocytes in the peripheral circulation were normal until the late stages when numerous myeloblasts appeared. Roentgenograms were made to exclude scurvy. There was no evidence of syphilis, and the diagnosis of leukemia was confirmed at necropsy. The diaphyses of the tubular bones were expanded due to external cortical thickening; double and even triple layers of cortical bone could be seen macroscopically. On microscopic examination, leukemic cells not only filled the medullary cavities but also overflowed their confines and lay between the various layers of the thickened cortex. Additional osteoblastic activity was evidenced by widening of the trabeculae and a generalized sclerosis. Similar changes were seen in the flat bones, the vertebrae and the ribs.

The fact that the skeleton is often affected in leukemia was noted anatomically and clinically during this same period by several authors, but except for the cases cited above, no mention was made of roentgenographic studies. Skeletal lesions in chloroma (which probably represents a variant of leukemia) had been more widely recognized,[13] yet Gould and LeWald[21] in 1916 believed the 2 cases they presented were the first in which the roentgen findings had been recorded. With respect to non-roentgenographic demonstration of osseous lesions in leukemia, Domarus[14] cited papers published in the first decade of this century which described rarefaction of bone, osteosclerosis, and periosteal infiltration and proliferation. Others are recorded by Forkner.[19] In 1913, Strauch[49] reviewed the literature on leukemia in childhood; among the symptoms he mentioned pains in the extremities and pain and swelling in the joints, "similar to articular rheumatism." The use of roentgenography was not discussed. As recently as 1933, Cooke[10] reported 50 cases of acute leukemia in children of whom 13 had rheumatoid pains; changes in the bones were not discussed either from a pathologic or roentgenographic standpoint.

Credit for the first case report in the American literature which described the skeletal lesions roentgenographically belongs to Abt[1] (1924). His patient, a five year old girl, had swelling over the right tibia for two months and pain in this region for two weeks, associated with fever and pallor. Only the cervical and supraclavicular lymph nodes were found to be enlarged; the spleen and liver were palpable just below the costal margin. The patient died three weeks later having had pain and tenderness over the left wrist, epistaxes and a purpuric skin eruption during her last days. The hemoglobin and red blood cells were depressed and the white blood cell count was low with a preponderance of small lymphocytes. Roentgenograms showed periosteal thickening in the upper third of the right tibia. At necropsy, proliferation of leukemic cells in the organs proved the diagnosis of leukemia. The periosteum over the right tibia was thickened. Microscopic examination revealed that leukemic cells filled the medullary cavity, from which bone trabeculae were missing. External to the compact cortical bone there was radial proliferation of new bone, the interstices of which were filled with young fibrous tissue and round cells. This, in turn, was covered with firm fibrous tissue (presumably the periosteum) and a layer of round cells. The destruction of the spongiosal trabeculae in this case contrasts with the sclerosis described by Oesterlin[40]; the external cortical thickening in each case, however, represents the same process whether the new bone is distributed radially or longitudinally in relation to the shaft.

The attention of roentgenologists was drawn to the skeletal manifestations of leukemia by Taylor[51] in 1926 who reported the case of the girl two years and ten months of age with progressive weakness and inability to walk for seven months. She had swelling of the legs and elbows, pallor, an enlarged spleen and generalized glandular enlargement. The white blood cells varied in number between 1,900 and

147,000 per cu. mm. with four "aleukemic periods." Roentgenograms of the legs demonstrated periosteal elevation; and, at necropsy, leukemic infiltration beneath the periosteum was observed. In 1927, Karelitz[29] described "Unusual Forms of Periosteal Elevation" in 2 children, one with metastatic neuroblastoma and the other with leukemia. The latter child was a three year old boy with weakness, swelling of the fingers, anemia and recurrent fever. Pain and swelling in the legs and right elbow occurred after admission to the hospital and responded only to transfusion. Because the white blood cells in the peripheral circulation were essentially normal in number and distribution until shortly before death, the periosteal proliferation raised the question of scurvy and syphilis. As the true nature of the disease became evident, internal cortical erosions of the left radius and right ulna appeared in roentgenograms in addition to the periosteal elevation previously observed in these and other bones. Necropsy was not obtained.

The roentgen features of diseases of the blood and hematopoietic system as they affect the bones were reviewed by Karshner[30] in 1928. In the discussion of leukemia, he referred to its association with bone pain and periosteal proliferation. Thereafter, reports of roentgenographic observations of skeletal involvement in leukemia became more frequent; and the several types of lesions, together with the morphologic changes producing them were described separately and in combination by various authors.

Poynton and Moncrieff[43] (1929) reported 2 children with a leukemia-like disease with subcutaneous nodules in the scalp. Both had pain and/or swelling in the joints, and roentgenograms demonstrated rarefaction of the bones in the regions where the pain was experienced. At that time the authors were reluctant to classify these cases as true leukemia, but it seems likely that they were. Appreciation of the frequency of bone lesions in leukemia would have provided support for the authors in the problem of diagnosis. In 1930, Baldridge and Awe[2] studied 150 cases of lymphoma and reported symptoms of acute arthritis in 13 of 20 cases under twenty-one years of age. The inaccuracy of the term arthritis will be discussed later, but the frequency of 65 per cent of young patients with bone pain is worth noting. That same year, Seward[45] reported the case of a thirty-one year old male with proved leukemia who complained of pain and swelling in the joints. Seward emphasized the joint pain in contradistinction to bone pain previously described, yet at necropsy the shoulder and elbow joints were normal grossly and microscopically. He reasoned therefore that invasion of the cancellous bone by leukemic cells was responsible for the pain referred to the adjacent joints. No roentgenograms had been made and no proof of osseous changes could be offered.

In 1931 Karshner[31] described a boy of two years and nine months who had pain and swelling of the left forearm just below the elbow associated with fever for three days. These complaints had been preceded by an upper respiratory infection a few days previously. On examination, the liver was palpable but not the spleen. Examination of the blood revealed an anemia; the red blood cells numbered 3,000,000 per cu. mm., the hemoglobin was 45 per cent of normal and the white blood cells numbered 7,800 per cu. mm. of which 15 per cent were polymorphonuclear leukocytes and 83 per cent, lymphocytes—mostly immature cells. No roentgenograms were made. The diagnosis was acute osteomyelitis. The left ulna was drilled but no pus or abnormal bone was found grossly and no microscopic examination of the material was made. The surgical wound healed normally. One month later, the child was readmitted because of fever and vomiting. He had a profound anemia, blood in the stools, petechiae, enlargement of the liver and spleen, generalized glandular enlargement and, like the cases of Poynton and Moncrieff,[43] nodules in the scalp. Blood findings were characteristic of leukemia. Roentgenograms taken during this second admission revealed cortical thickening at the upper end of the left ulna, beneath which there was bone destruction. Porous destruction was described in the distal metaphyses of both bones of the forearm, all the metaphyses of the humeri, in the ribs, pelvis and upper ends of the femora. Periosteal proliferation was observed at the upper end of the left humerus, external to the destructive lesions. Karshner stated that this case was similar in all respects to 5 other cases he had seen, 4 of which were proved to be leukemia by postmortem examination.

Trusen[52] (1931) described the case of a five and a half year old boy with pain and swelling in the extremities as well as in the lymph nodes, one testicle and the parotid glands. A leukopenia was present. The diagnosis of leukemia was established by biopsy of a supraclavicular lymph node and confirmed at

necropsy. Roentgenograms during life revealed cortical thickening of the left femur and a spontaneous fracture through an area of demineralization in the right femur. Transverse bands of diminished density were present in the ends of the shafts of the femurs. Microscopic examination of the affected bones showed that the leukemic "infiltration" extended through the haversian canal from the medullary cavity and raised and infiltrated the periosteum. At a meeting of the American Pediatric Society in May, 1932, Wollstein[55] summarized the findings in 28 cases of leukemia in children seen at Babies Hospital in the preceding eight years. These cases are included in the present report. Wollstein found that pains over the bones occurred in 10 of the 28 children; and 6 had positive roentgenographic findings, namely, rarefaction, destruction and elevation of the cortex of affected bones. Poynton and Lightwood[42] (1932) reported pain, roentgenographic bone lesions and the autopsy findings in a three year seven month old girl whose clinical course simulated acute rheumatism. Gittins[20] (1933) stated that bone changes in leukemia were rare and noted lesions only once in the 14 cases he reported. He rightly emphasized the frequency of the aleukemic phase in children and on that basis suggested the term leukosis as preferable to leukemia. Gittins illustrated the difficulties of differential diagnosis by presenting a case of congenital syphilis in a three month old infant with a leukemoid blood picture. Baldridge and Fowler[3] (1933) also found the term leukemia unsatisfactory and offered "aleukemic myelosis" as one more suitable. Under this title they reported 11 cases of myeloid hyperplasia in 2 children and 9 adults. Not all these could be classified as leukemia, but 7 of the 11 had bone pain, and 5 had bone lesions demonstrable by roentgenographic examination. Among a list of circumstances which the authors said should suggest the possibility of hematopoietic disease in the absence of a leukemic blood picture, they included arthritic symptoms, deep bone pain and lytic lesions in bone.

Pain and swelling of the extremities were so prominent a feature of the case reported by Smith[47] (1933) that he believed arthritis was present. His patient was a three year old boy who had four hospital admissions during the thirteen months of illness. Migratory polyarthralgia and swelling of the small joints as well as the large joints of the extremities were thought to represent manifestations of rheumatic fever because the peripheral blood picture did not suggest leukemia. Lack of response to salicylates and improvement after transfusions (as in Karelitz's[29] case) led to a lymph node biopsy which was characteristic of leukemia. Roentgenograms of the long bones demonstrated atrophy and thinning of the cortex with erosion and periosteal thickening at the ends of the bones and medullary rarefaction. Osteoporosis was observed at the ends of the shafts of several bones. At necropsy the diagnosis of leukemia was confirmed; no Aschoff bodies were found. The joints were not examined. Sutton and Bosworth[50] (1934) were also impressed with the rheumatic-like symptoms in a two year eight month old girl with pain and swelling in several joints. The diagnosis of leukemia was made at the third hospital admission after a lymph node biopsy. During the earlier admissions the absence of abnormal cells in the peripheral circulation and the normal size of the liver and spleen lessened the probability of leukemia. The authors doubted the diagnosis of rheumatic fever clinically because they could not conceive the heart escaping injury when the joint symptoms were so severe.

Coexistent rheumatic fever and leukemia was described by Ehrlich and Forer[16] (1934). They observed an eleven and a half year old girl with pain in the lower left arm of two months' duration; fusiform swelling was present and periosteal new bone formation was seen in roentgenograms. Tonsillectomy and dental extractions were performed in an effort to remove possible foci of infection for what was considered to be arthritis. Following these procedures, the patient developed fever and a polyarthritis which responded to salicylates. A heart murmur appeared and then, for the first time, abnormal white blood cells were observed in the peripheral circulation associated with rapid enlargement of the liver, spleen and lymph nodes. The course thereafter was rapidly retrogressive. Abnormal white blood cells were found in increasing numbers in the circulating blood; a lymph node biopsy was characteristic of leukemia and this diagnosis was confirmed at necropsy. The necropsy showed, in addition, fresh vegetations on the mitral valve and Aschoff bodies in the myocardium. Leukemic infiltration, periosteal elevation and subperiosteal new bone formation accounted for the changes seen in the roentgenograms.

One of the first reviews of bone changes in leukemia was that of Snelling and Brown[48a] and of Erb[17] (1934). These authors tabulated the findings in 12 cases of leukemia showing bone changes. The types of lesions found were listed and the differential diagnosis was discussed. Pertinent reports from the literature were reviewed. The pathologic discussion by Erb[17] was particularly interesting. He described five types of pathologic changes from a study of [illegible] of their cases: infiltration, rarefaction, proliferation, degeneration and hemorrhage. Discussion of the origin of the leukemic cells was avoided, but Erb considered the accumulations in the bones and under the periosteum as metastases. As a result of pressure and/or osteolytic ferments bone trabeculae disappeared at sites of accumulation of leukemic cells; the region of the cartilage-shaft junction was a common location for such changes. According to Erb, new bone formation occurred only in the subperiosteal region as the result of periosteal elevation by leukemic cells coming through the haversian canals. He made no mention of endosteal sclerosis. Bone pain was explained on the basis of increased intra-osseous pressure due to "infiltration." It mattered little whether this took place within the medullary cavity, the haversian system or under the periosteum. The close relationship between the periosteum and the joint ligaments was considered as the mechanism of referred joint pain.

In a second paper, Smith[48] (1935) reported 3 cases of leukemia in children with rheumatic symptoms and no bone lesions demonstrable in the roentgenograms. All 3 were thought to have rheumatic fever since enlargement of the spleen, liver and lymph nodes, as well as the appearance of abnormal circulating white blood cells, occurred late if at all. All 3 patients had cardiac murmurs, a clinical feature present in many of the reports already described. Smith attempted to differentiate this group from those with roentgenographic lesions and again used the unfortunate term "arthritis" to describe the latter group. Craver and Copeland[12] (1935) reviewed the records of 168 patients with leukemia seen at Memorial Hospital and found 7 with bone changes demonstrated in roentgenograms. The associated pathologic changes were similar to those described by previous investigators. Many areas of medullary bone erosion were found at necropsy that were not demonstrated roentgenographically. This led Craver and Copeland to believe that the changes seen in roentgenograms represented lesions of relatively long duration. They also suggested that their figures concerning the incidence of such findings were deceptively low inasmuch as roentgenographic studies in patients with leukemia had not been routine. An atypical blood picture for leukemia, particularly a leukopenia, was present in all 7 cases. This suggested that gross bone involvement was more common in the aleukemic forms of leukemia. The effect of the age of the patients was not considered. Doub and Hartman[15] (1935), in a discussion of the roentgen diagnosis and treatment of lymphocytic, myelocytic and monocytic neoplasms, emphasized the bone changes in this group of diseases. Changes were most marked and found most frequently in lymphatic leukemia and corresponded to the types of changes already noted. The need for roentgenographic studies in all cases of leukemia with pain or swelling over the bones and joints was stressed.

A frequently cited study of the bone changes in leukemia in children is that of Baty and Vogt[4] (1935). This was the first study of a large number of children in which roentgenographic examinations were available for statistical analysis. Bone changes demonstrable by roentgenography were found in 43 of 60 patients, an incidence of over 70 per cent. The most frequent change was a narrow transverse zone of diminished density at the end of the shaft of the long bones. Trusen,[52] Smith,[47] Snelling and Brown[48a] and Erb[17] had described similar findings; Baty and Vogt pointed out that the zones were most marked in bones where growth was rapid, and became more prominent as the disease progressed. The nonspecificity of these zones was appreciated. Similar findings had been observed in patients suspected of having aleukemic leukemia clinically but not confirmed at autopsy; these patients died of septicemia. The zones had also been seen in a three year old child with streptococcic meningitis and a four year old child with a cerebellar tumor. Neither had evidence of leukemia. The possibility of a metabolic disturbance with a secondary disturbance of bone growth was considered as the mechanism; associated local infiltration by leukemic cells could contribute to the picture. Periosteal elevation and bone erosion were rare in their experience. The differential diagnosis of lytic bone lesions was discussed and the value of roentgen examination in aleukemic or atypical cases of leukemia was emphasized.

Osteosclerosis was not present in the cases studied.

Marked osteolytic changes in an eight year old girl with leukemia were described by Clark[7] (1936). The illness began with bleeding following a dental extraction three months before admission to the hospital; this was succeeded by pallor, listlessness and ecchymoses. One month before admission severe pain in the lumbar region confined the child to bed. Physical examination on admission disclosed pallor, a systolic heart murmur and a palpable liver. The spleen and the lymph nodes were not enlarged. Blood findings were normal except for the anemia. Roentgenograms showed marked patchy decalcification of the pelvic bones and femurs; both femoral heads were separated from the shafts and a pathologic intertrochanteric fracture was present on the right. There were multiple erosions of the skull, ribs and spine. Bone resorption was extensive at the ends of the shafts of the long bones with beginning epiphyseal separation. The serum calcium was increased. No Bence-Jones protein was found in the urine. The parathyroids were explored surgically and were normal. Four days after the operation, the true diagnosis became evident when the white blood cells rose to 25,000 per cu. mm. of which 69 per cent were small lymphocytes. These rapidly increased to 88 per cent and terminally numbered 96 per cent of the total circulating white blood cells. There may be some question concerning the diagnosis in this case as anatomic proof was lacking, but it serves to illustrate the type of obscure clinical picture in which the diagnosis of leukemia should be considered.

Even in the presence of confirmatory anatomic findings Conybeare[9] (1936) accepted the diagnosis of leukemia cautiously in his case. The patient, an eight year old girl, had multiple joint pains and fever for one year following chronic mastoid infection and was believed to have rheumatic fever. The presence of lymphoblasts without leukocytosis was interpreted as a leukemoid response to infection. Still's disease was considered when an earlier response to salicylates was lost and lymph nodes, liver and spleen enlarged. The large joints were swollen and tender and the muscles were wasted; there were fusiform swellings of the shafts of the proximal phalanges without joint involvement and similar changes in the neighborhood of large joints. No articular effusions were present. Roentgenograms showed slight periosteal elevation over one ulna. At necropsy extensive leukemic infiltration was observed in all the organs. The only morbid changes in the joints were small hemorrhagic areas on the articular surfaces of one tibia and femur at the knee. No microscopic examination was made of these lesions. This is unfortunate since this case and that reported by Seward[45] were the only ones in which examination of the joints was reported up to that time.

Additional reports of skeletal lesions in leukemia observed in roentgenograms were presented by Lyon[37] (1936), Connor[8] (1937), and Lövgren and Eden[36] (1938). The variations in the clinical picture and the difficulties of diagnosis were brought out in an excellent review article by Jackson[25] (1939). Mendl and Saxl[38] (1940) described 2 cases of skeletal leukemia in children and 1 in an adult. Several other reports in the foreign literature were reviewed in their paper. In a discussion of the atypical manifestations of leukemia, Wintrobe and Mitchell[54] (1940) included symptoms referable to the bones and joints, with occasional roentgenographic findings. Postmortem examination of clinically affected joints was made in several of the cases but no significant changes were found. Kositchek[34] (1943) reported osteolytic lesions in a nineteen year old male with monocytic leukemia; all previous cases of leukemia had been diagnosed as lymphocytic or myelocytic or had not been classified.

Falkenstein and Fowler[18] (1943) reviewed the clinical data in 61 cases of leukemia in children. The frequency of "aleukemic" or "subleukemic" types was remarked. Setting the arbitrary standard that total white blood cell counts of less than 12,000 cells per cu. mm. would be considered "aleukemic," 27 cases were found to be "aleukemic" and 32 cases were "leukemic"; 2 cases were not classified. Three of the 27 "aleukemic" cases became "leukemic" and 4 of the 32 "leukemic" cases had an "aleukemic" phase. No appreciable differences in the necropsy findings were noted in the two types of cases, nor were there any essential differences in the onset, course and symptoms. Kalayjian, Herbut and Erf[28] (1946) reviewed the four types of lesions found in the literature and added 2 cases with typical hematologic, roentgen and necropsy lesions. Twenty-nine additional cases were recorded by Landolt[35] (1946). Forty-eight cases of leukemia were included in this report; roentgenograms were made in only 38, giving an incidence of demon-

strable bone lesions of over 75 per cent in those studied by this method. The general subject of skeletal lesions in leukemia is well covered in these last three reviews.

PRESENTATION OF DATA

Criteria for Selection of Cases. The definition of leukemia as a fatal proliferative disease of the blood-forming organs associated with the presence, at some time, of immature leukocytes in the circulating blood could not be applied to all cases. Many patients were admitted for diagnosis or confirmation of the diagnosis made elsewhere, and were then discharged for terminal care at home; the necessary fatal outcome could not be ascertained. Necropsy proof likewise was available in only a small percentage of our cases, largely for the same reason. Moreover, the dividing line between "myeloid hyperplasia" and "leukemia" is not clear, and where the pathologist used the former term and not the latter, it was considered best to omit the case from consideration. Even the presence of immature leukocytes in the circulating blood was inadequate as an unequivocal diagnostic sign since such cells were found in some patients who, at necropsy, showed no evidence of leukemia; and in 1 leukemic patient (necropsy) no immature leukocytes adequate for hematologic diagnosis were found in a long series of blood counts.

The cases of leukemia reported here include those whose clinical, hematologic or necropsy findings, singly or in combination, warranted the diagnosis in the face of the above reservations. Bone marrow biopsies were of great value where recorded. In general, the cases accepted as suitable for review presented some combination of the following factors: a clinical course characterized by fever, pallor, listlessness, hemorrhagic tendencies, enlargement of the liver, spleen and lymph nodes, and a fatal outcome; hematologic findings of immature white blood cells in the peripheral circulation, anemia, reduction of platelets and a bone marrow biopsy in which normal cells were crowded out by abnormal cells; and necropsy findings of leukopoietic hyperplasia with the presence of immature leukocytes in abnormal locations, e.g., kidney, testicle, intestine or skin. The presence of other disease which might produce these signs and symptoms was excluded to a reasonable degree of probability.

Roentgen Criteria. Roentgenograms of the appendicular skeleton were considered adequate for this study. The few cases in which lesions were present in the axial skeleton, as in ribs on a chest film, were included in the absence of roentgenograms of the extremities. If leukemic lesions were not found in the axial skeleton and roentgenograms of the extremities were not available, the case was not included.

Table I

AGE AND SEX INCIDENCE OF CASES STUDIED

Total cases of leukemia			131
Cases with adequate roentgen studies			103
Male	69	Female	34
Age: Less than 1 year			5
1 through 4 years			62
5 through 9 years			24
10 years and over			12

Incidence (Table I). The findings in 131 leukemic patients admitted to Babies Hospital during the period 1924 through 1946 were suitable for review; 103 of these had satisfactory roentgenograms. No attempt has been made to classify the cases with regard to cell type. There were 69 males and 34 females. The two-to-one preponderance of males is in agreement with most other reports.[4,18,35,55] The ages at onset of symptoms varied from twenty-two days to twelve years and seven months; 62 (60 per cent) had their onset between their first and fifth birthdays. Children are not admitted to Babies Hospital after their thirteenth birthday.

Clinical Features. In 60 cases satisfactory data were available for an estimation of the duration of the illness (Table II).

TABLE II

DURATION OF ILLNESS

Cases with known duration			60
Less than 1 month	6	7 to 8 months	3
1 to 2 months	11	8 to 9 months	4
2 to 3 months	9	9 to 10 months	3
3 to 4 months	7	10 to 11 months	2
4 to 5 months	4	11 to 12 months	1
5 to 6 months	8	12 to 13 months	1
6 to 7 months	3	14 months	1
		18 months	1
Average duration			5.1 months

Such an estimation required knowledge of the time of death and the assumption that the onset of the disease corresponded roughly to the time of appearance of the first clinical symptoms. Since the onset was often vague and indefinite, the results are only approximations. More than 70 per cent of the patients died within seven months after the clinical onset of their disease. The shortest duration was eleven days in a case of "congenital leukemia"; symptoms began on the twenty-second day of life. This case has been reported in detail by Kelsey and Andersen.[32] The longest duration was eighteen months in a five and a half year old girl. The average duration was 5.1 months.

The frequency of the cardinal clinical signs and symptoms as found in the 103 cases is shown in Table III. Early diagnosis and discharge from the hospital of some patients undoubtedly reduced the incidence of some of the manifestations as scored. It is noteworthy that any one of the signs and symptoms may be absent in a given case; many cases lacked more than one.

TABLE III

FREQUENCY OF CLINICAL SIGNS AND SYMPTOMS OBSERVED IN 103 PATIENTS

	Cases
Pallor	98
Fever	94
Listlessness	92
Enlarged spleen	90
Enlarged liver	89
Generalized lymph node enlargement	84
Hemorrhagic tendencies	82
Bone pain	42
Ophthalmoscopic examination recorded	33
Retinal hemorrhages present	14
Retinal hemorrhages absent	19

Hematologic Data. As previously mentioned, no attempt was made to classify the cases according to cell type. The records were reviewed, however, with regard to the presence or absence of abnormal leukocytes in the circulating blood and to the total numbers of white blood cells per cubic millimeter. The arbitrary number of 12,000 white blood cells per cu. mm. was accepted as the standard dividing line between high and low counts, and their frequency is tabulated in Table IV.

TABLE IV

TRENDS IN TOTAL WHITE BLOOD CELL COUNTS

Immature cells present	102 patients
No immature cells	1 patient

	Patients
Persistently high*	40
Persistently low	27
High to low	12
Low to high	24

* 12,000 white blood cells per cu. mm. taken as the arbitrary dividing line between high and low counts.

Abnormal white blood cells were found in the peripheral circulation in 102 of the 103 cases. The 1 case in which no abnormal forms were found was that of a four year two month old girl who had been weak, feverish and anemic for seven months, and who was admitted to the hospital because of severe, recurring epistaxes of five days' duration. During two previous admissions at another hospital where transfusions had been given, blood counts had shown a profound anemia with pancytopenia. The white blood cells numbered 4,550 per cu. mm. as a maximum and averaged about 2,000 per cu. mm. for thirteen determina-

tions. The polymorphonuclear cells varied between 3 and 56 per cent, but were generally under 30 per cent with correspondingly larger numbers of lymphocytes. On one occasion a single myelocyte was described, on another "stab and juvenile forms" and on a third "very young forms." At Babies Hospital, where the patient died one week after admission, four blood counts failed to demonstrate any abnormal white blood cells. The lymphocytes, which varied between 88 and 96 per cent of the total white count (highest count, 1,350 per cu. mm.), were not considered abnormal. Schilling counts of the polymorphonuclear cells were 0–6–0, 2–6–0 and 0–6–0. The diagnosis of leukemia was established at necropsy. Although there may be some objection to including this case as one in which no abnormal white blood cells were found, the possibility of such a happening is strengthened by the findings here.

The absence of leukocytosis is more common than the absence of abnormal leukocytes. The repetitious reference to "aleukemic leukemia" in the literature reviewed, suggests a tacit appreciation of this feature of the disease. Washburn[53] in 1925 stressed the findings of a persistent leukopenia in leukemia and deplored the use of the term "aleukemic leukemia." Falkenstein and Fowler[18] found 27 of 59 cases analyzed to have total white blood cell counts consistently under 12,000 per cu. mm., and 4 of the 32 remaining cases had "aleukemic phases." In the present series, 27 of the 103 cases had total white cell counts consistently under 12,000 per cu. mm. and 36 additional cases had similar counts either early or late in the disease.

The presence of an increased erythrocyte sedimentation rate was a related finding in almost all cases. In 6 cases the erythrocyte sedimentation rate was normal early in the disease, but in all cases in which this examination was repeated, significant increases were recorded.

Roentgenographic Data. Fifty-two of 103 leukemic children showed bone changes in their roentgenograms; four types of lesions were found: transverse bands of diminished density, osteolysis, osteosclerosis and subperiosteal new bone formation. Their incidence and relationship to pain are indicated in Table v. All four types have been described previously in the literature. Frequently, more than one type of lesion was present in a single patient; the figures pertaining to the types of lesions indicate the number of times each lesion was observed and consequently the total number of lesions does not correspond to the total number of cases with lesions.

TABLE V

CORRELATION OF PAIN AND ROENTGEN FINDINGS IN BONES

	Patients
Pain present	42
Pain with lesions	25
Pain without lesions	17
Roentgen lesions present	52
Lesions with pain	25
Lesions without pain	27

Type of lesion	With pain	Without pain	Total
Transverse band	4	10	14
Osteolysis	21	18	39
Osteosclerosis	6	3	9
Subperiosteal new bone	12	5	17

No lesions and no pain ..... 34 patients

As in the case of figures on the incidence of the clinical signs and symptoms, the tabulated incidence of skeletal lesions represents only the findings in a selected group of cases modified by a multitude of factors. The chief modifying factor is the time the roentgenograms were made in relation to the beginning or the end of the illness. The appearance of roentgen lesions in some cases in which serial studies were made indicates that lesions are more numerous in the later stages of the disease. Since many patients left the hospital relatively early in their illness, lesions which may have developed subsequently were not demon-

FIG. 1. Transverse bands of diminished density at the ends of the shafts in a four year old boy with classical leukemia. Similar findings were present in other long bones.

strated. The omission of routine roentgen investigation of patients with leukemia probably accounts for the general lack of recognition of the frequency of this manifestation of leukemia.

TABLE VI

DIAGNOSES CONSIDERED MORE THAN ONCE IN 103 INFANTS AND CHILDREN WITH LEUKEMIA

	Times
Rheumatic fever	9
Secondary anemia	9
Still's disease	5
Infectious mononucleosis	5
Banti's disease	4
Sepsis	3
Hodgkin's disease	3
Sickle cell anemia	2
Subacute bacterial endocarditis	2
Purpura (idiopathic)	2
Lymphosarcoma	2

Forty-two patients complained of pain; 25 had skeletal lesions demonstrable in roentgenograms; and in 17, lesions were not found. The pain varied from mild malaise to severe, sharply localized pain in one or several sites. Frequently it was characterized as "pain in the bones" and occasionally it was associated with local swelling. It was this latter type of reaction which led Smith[47,48] and others[9,42] to interject the term "arthritis."

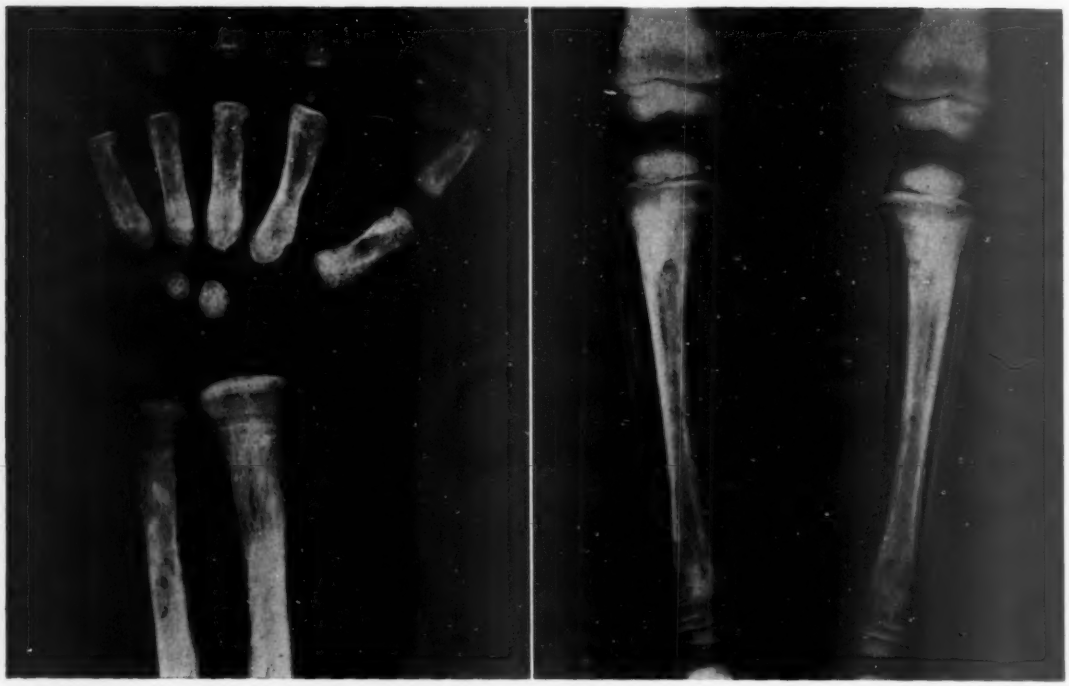
The cause of pain is not certain; it is reasonable to assume that the pressure of rapidly proliferating leukemic cells on adjacent nerves and blood vessels may be responsible. The rigid bone and the tough periosteum do not permit expansion to the degree that soft tissue does, and intraosseous or subperiosteal pressure increases in proportion to the rapidity of proliferation. So-called "joint pain" probably results from pain referred from lesions adjacent to the joint in question. Erb[17] and Seward[45] called attention to the intimate relationship between the periosteum of a long bone and the capsule of its contiguous joint. Examination of affected joints at necropsy has been infrequent; in 2 cases in which such examination was reported[9,45] no pathologic findings were observed. Wintrobe and Mitchell[54] did not report their necropsies in detail, but stated that in the cases in which joints were examined, no abnormalities were visible. The use of the term "arthritis" in such cases is misleading.

No significant correlation was observed between the sites of pain and the sites of roentgen lesions. The size of the lesion was probably the deciding factor in its roentgen recognition and pain from pressure could easily occur in minute lesions. Craver and Copeland[12] found small lesions at necropsy which could not be demonstrated on roentgenograms. The fact that 17 patients in this series complained of pain but showed no roentgen lesions can be explained on this basis.

Of the 52 patients with roentgen lesions, 25 had pain and 27 had no pain. The latter group lends further support to the belief that the incidence of skeletal lesions is greater than is generally appreciated. Thirty-four of the 103 patients had no roentgen lesions and no skeletal pain.

Transverse bands of diminished density (Fig. 1) occurred at the ends of the shafts of long bones in 14 patients. These often were the first lesions to appear when more than one type was present in a single case. They were best demonstrated in the tibias and femurs at the knees. As a general rule, they occurred at the sites of rapid growth and were often well marked in the distal ends of the radius and ulna. Occasionally, similar lesions were seen in the bases of the phalanges. Transverse bands appeared between four and ten weeks after the onset of symptoms. Figure 2*A* demonstrates no abnormalities in the tibias thirty days after the onset in a two and a half year old girl; distinct transverse bands were present in the roentgenograms made six weeks later (Fig. 2*B*). It is difficult in many cases to decide at what point a "transverse band" becomes an osteolytic lesion. Figure 3 illustrates this difficulty. There is no doubt, in view of the irregular demineralization adjacent to the transverse band in Figure 3*B*, that this shadow represents osteolysis. The anatomical basis for the transverse band shadow is not known with certainty. Two factors probably are concerned: one, nutritional and nonspecific; and the other, focal bone destruction due to pressure of proliferating abnormal leukocytes. Baty and Vogt,[4] who found the transverse radiolucent band to be the most common type of lesion in their series, recognized the two possibilities and supported the former by

Fig. 2. Speed of development of lesions in leukemia. *A*, roentgenogram taken thirty days after onset of symptoms. Very faint transverse bands are present in the tibias but no distinct changes are seen. *B*, roentgenogram six weeks later. Extensive destructive and productive changes have taken place. Transverse bands at the ends of the shaft stand out and focal osteolytic changes are present in the subjacent metaphyses. Note the subperiosteal new bone formation in the left fibula which simulates splitting of the cortex.



A *B*

FIG. 3. Case 1, aged two years two months. Clinical course suggested rheumatic fever or rheumatoid arthritis. Blood smears were normal at the times these films were made. Marrow aspiration immediately afterward was characteristic of leukemia, and subsequently, immature cells appeared in the peripheral circulation. Deep transverse bands are seen in the metaphyses and osteolytic and osteosclerotic lesions in the shafts. Note the cortical erosions in the metacarpal bones.

citing cases of critically ill patients with other diseases in whom similar changes were present. Erb[17] and others[28,35] provided pathologic proof of focal osteolytic changes associated with the presence of large numbers of abnormal leukocytes in the regions corresponding to the sites of the transverse bands. Erb even raised the question of an osteolytic ferment being secreted by these cells. It would seem more likely that the pressure of the rapid cellular proliferation on the adjacent trabeculae and their blood vessels is responsible for the disappearance of bone. Extensive leukemic proliferation is frequently found in the medullary cavity unassociated with destructive bone lesions. These cells are identical with those found in lesions. If an osteolytic ferment were produced by the cells, lysis should occur wherever the cells are found. The focal nature of lesions suggests that local factors, e.g., pressure and vascular supply, are the important agents.

It is possible that the bony defects responsible for transverse bands are reversible. Transverse bands disappeared in 2 of our patients. One, a six and a half year old girl, had faint bands in her long bones which disappeared during a remission of the disease when the child's nutrition improved perceptibly. The other was a two year old boy whose transverse bands appeared during two weeks' observation and then faded while he was being treated with penicillin for a secondary infection. In the latter patient tibial biopsy and necropsy proved the diagnosis.

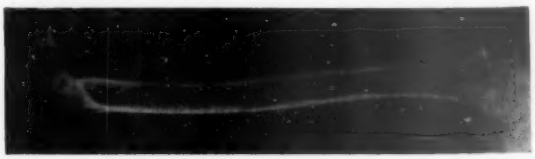


FIG. 4. Osteolytic lesions in leukemia. Multiple focal lytic lesions are present, producing "moth eaten rarefaction." Subperiosteal new bone formation is also observed.

Osteolytic lesions occurred in 39 patients; in 75 per cent of all patients with lesions and 50 per cent of all lesions observed. Both focal and diffuse destructive lesions were noted. Focal lesions were characterized by areas of radiolucency in the spongiosa (Fig. 4). Some were sharply circumscribed, others had indefinite margins. An occasional lesion, seen in profile, demonstrated that internal erosion of the cortex also occurred. The "moth-eaten" appearance of some bones probably resulted from destruction of both spongy and compact bone. Conglomerations of such lesions produced diffuse osteolysis in some cases. In others (Fig. 5) extreme degrees of osteolysis occurred and resulted in fractures. None of the cases at admission had spontaneous fractures, although this complication has been reported elsewhere.[52] The skull and pelvis were involved occasionally. Exaggeration of the normal diploic pattern could be seen in the skull, but owing to the great normal variation this feature was interpreted with difficulty. In the pelvis, a coarse reticulated pattern was more easily recognized as pathologic. In cases demonstrating marked osteolysis, elevation of the blood calcium content was a frequent associated finding. The levels of phosphorus and phosphatase were not appreciably altered. Two patients with leukemia had focal areas of diminished density in the bones of the lower extremity which were identical roentgenographically with the cortical defects described in normal, or at least non-leukemic individuals by Sontag and Pyle,[46] Hatcher,[22] and Caffey.[5]

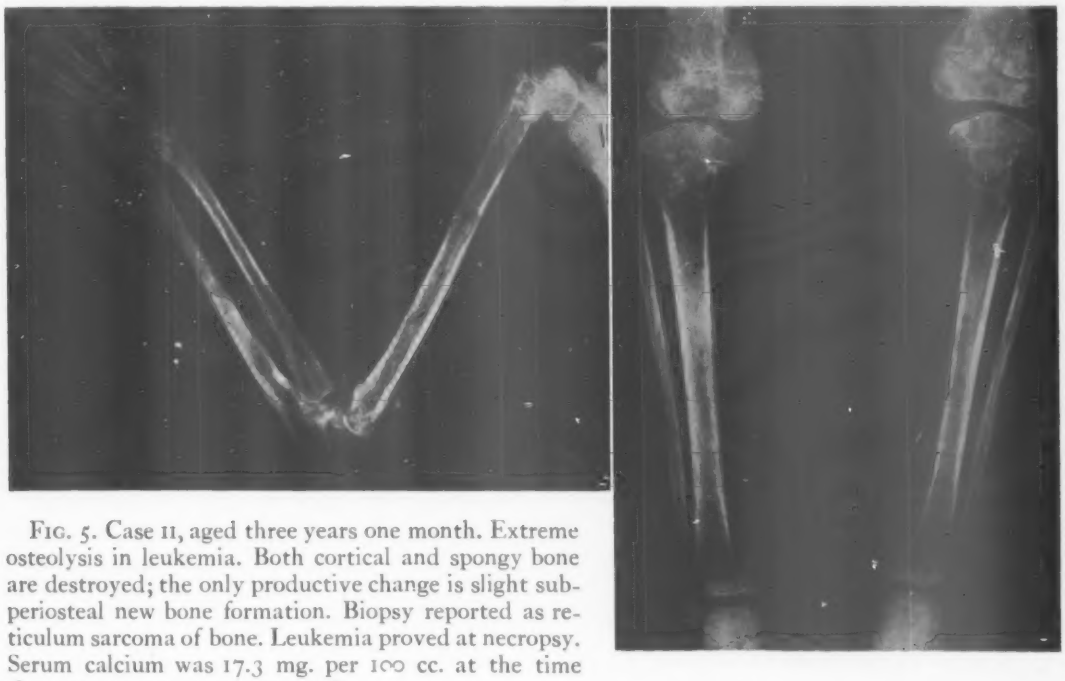


Fig. 5. Case 11, aged three years one month. Extreme osteolysis in leukemia. Both cortical and spongy bone are destroyed; the only productive change is slight subperiosteal new bone formation. Biopsy reported as reticulum sarcoma of bone. Leukemia proved at necropsy. Serum calcium was 17.3 mg. per 100 cc. at the time these roentgenograms were made.

Osteosclerosis was the least frequent of the four types of lesions; it was found in 9 patients. Like osteolysis, it was either focal or diffuse. Osteosclerosis was more difficult to assess when it was found in association with lytic lesions because of contrast. Figure 6 represents generalized osteosclerosis in a four and a half year old girl.

Subperiosteal new bone formation (Fig. 7) was observed in 17 cases. This type of lesion was of great interest to earlier observers because of its supposed rarity, but the number of case reports presenting this finding indicates that it is one of the more frequent lesions in leukemia. It was second in frequency in this series, occurring in one-

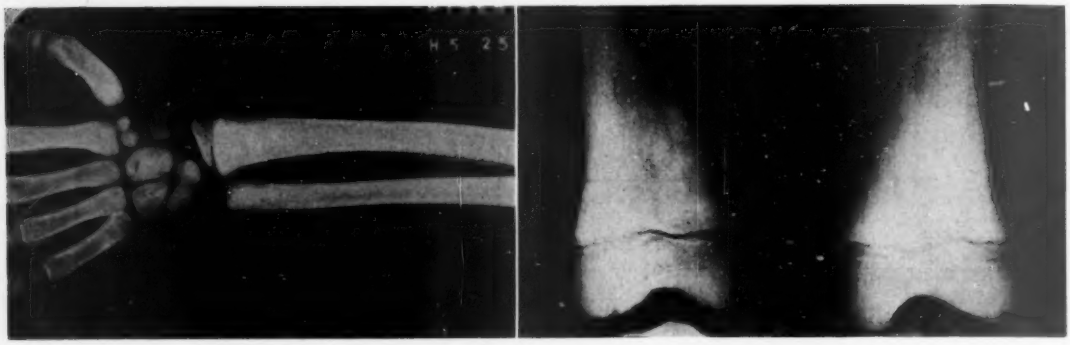


Fig. 6. Osteosclerosis in leukemia. The increased density is due to heavy spongiosa rather than cortical thickening.

third of the cases. The cortical thickening it produces was seen in all the major long bones, less frequently in the ribs and the small tubular bones of the hands and feet, and rarely in the flat bones.

Associated roentgen findings outside of the skeletal system which were often helpful in diagnosis were enlargements of the lymph nodes, mediastinal tumors and enlargement of the adenoids. Soft tissue swellings in the neck and axilla were often observed as incidental findings in chest roentgenograms; mediastinal widening and leukemic proliferation in the lungs occurred much less frequently. Lateral projections of the neck occasionally demonstrated large lobulated soft tissue shadows projecting into the nasopharyngeal air column from the posterior pharyngeal wall in the position normally associated with the adenoids. None of these findings was specific for leukemia, but they suggested that a systemic disease was operative and that lymphatic structures were involved in a proliferative reaction.

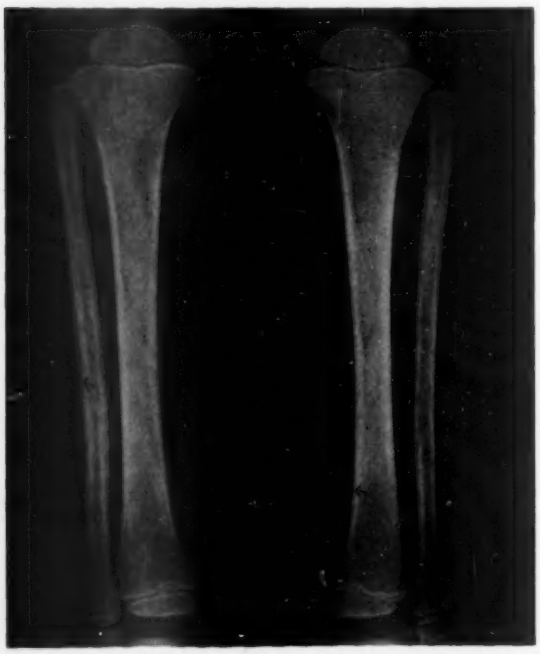


Fig. 7. Subperiosteal new bone formation in leukemia. The periosteum has been elevated by proliferating leukemic cells and has produced new bone on its internal surface.

Morbid Anatomy. The anatomical basis for the lesions has been established[16,17,28,38] and the few cases in this series in which microscopic examination of bone was recorded conformed in all respects with the descriptions given in the literature. The destructive lesions have been discussed briefly in association with their roentgen counterparts, the transverse band of diminished density and osteolysis. The productive lesions, osteosclerosis and subperiosteal new bone formation, depend on the stimulation of bone-producing cells by the proliferating leukemic cells. In the former case, the endosteal osteoblasts produce heavier trabeculae; in the latter, the osteoblasts of the periosteum form a layer of new bone over the masses of leukemic cells which separate the periosteum from its underlying cortex. The maturation of leukemic cells to osteoblasts postulated by Erf[28] is an unnecessary assumption. The production of

bone by osteoblasts may be altered in two directions so far as the roentgen shadows are concerned: an increase or a decrease in comparison with normal. If stimulation of bone production predominates we have osteosclerosis; if decreased production results, there is osteolysis. The disturbance of osteogenesis as seen in roentgenograms is similar to that in many bone infections and in other neoplasms either primary or secondary in bone; destruction or production or both may be present, although one may be the more common finding.

Differential Diagnosis. The preliminary clinical diagnoses in the 103 cases of leukemia indicate the conditions most likely to be confused with this disease. The most common diagnoses are listed in Table VI. Diseases characterized by fever, anemia and arthralgia predominate. Rheumatic fever was the most frequent and secondary anemia was second. The frequent finding of a cardiac systolic murmur, the pains and swelling of the extremities, anemia, increased erythrocyte sedimentation rate and occasional rashes made rheumatism a reasonable possibility in the absence of abnormal circulating leukocytes. Several features are of value in the differentiation of rheumatic fever and leukemia. The age distribution is generally younger in leukemia. Pains and swellings in the extremities do not show the usual prompt response to salicylates and almost invariably do respond to transfusion. The finding in the bones of roentgen lesions of any of the four types described excludes rheumatic fever. Concurrent rheumatic fever and leukemia, as in the patient described by Ehrlich and Forer,[16] are a medical curiosity and diagnosis must await necropsy.

"Secondary anemia" was a second clinical diagnosis. The usual primary factors were malnutrition, infection and poisoning due to drugs. In the absence of abnormal leukocytes in the peripheral circulation, the finding of skeletal lesions in roentgenograms is an invaluable diagnostic aid. However, more caution must be exercised since destructive and productive bone lesions may be due to infection, and infection in children may be the cause of immature leukocytes in the peripheral circulation. Moreover infection is not uncommon in children with leukemia. The failure of the patient to respond to the usual therapy for the primary cause of the anemia should lead one to look further for a diagnosis. It is possible that a coincident spontaneous remission in leukemia may simulate a response to therapy and the true diagnosis is obscured until signs and symptoms recur. Bone marrow biopsy can be of great assistance here provided the uncertainty of the standards for infants' bone marrow is appreciated. Mineralization of the sternum in infants is subject to great variation and even in widespread disease of the bone marrow this bone may be an inadequate site for biopsy. The sites of bone lesions seen in roentgenograms offer the best chance for diagnosis in such cases.

Still's disease and infectious mononucleosis were next in frequency among the diagnoses considered in cases of leukemia. The former was considered because of the arthralgia, anemia and splenomegaly and the latter because of the peculiar blood picture and enlargement of the spleen and lymph nodes. From the roentgen standpoint, thickening of the small tubular bones of the hands and feet in Still's disease may simulate leukemia in its early stages. However, articular cartilages are not destroyed in leukemia and they are always partially destroyed in Still's disease. The relatively benign course and confirmatory heterophile agglutination test serve to identify infectious mononucleosis. There are no bone changes in infectious mononucleosis.

Banti's syndrome entered into consideration because of splenomegaly, anemia and gastrointestinal hemorrhages in 4 patients. The blood picture and the demonstration of esophageal varices should be helpful in the differential diagnosis. The appearance of other signs of leukemia led to the correct diagnosis in the 4 cases. Hodgkin's disease offered difficulties in diagnosis by

Fig. 8. Case v, aged two years three months. Transverse bands of diminished density in disseminated tuberculosis. Fever, pallor and leukemoid blood picture. No evidence of leukemia at necropsy, but extensive tuberculous involvement of bone marrow.

virtue of the lymph node enlargement and anemia; biopsy of affected lymph nodes was more valuable in recognizing leukemia than in ruling out Hodgkin's disease. Bone lesions described in adults with Hodgkin's disease are rare in children, probably because the disease itself is uncommon in children.

Sepsis was incorrectly considered only a third as often as rheumatic fever yet is one of the diseases most easily confused with leukemia. Among the cases originally diagnosed leukemia and discarded from the group under consideration were several whose subsequent course or necropsy findings proved the presence of infection and the absence of leukemia. All had clinical and laboratory signs of leukemia, 2 had positive blood cultures and hypoplastic marrow and one had "practically conclusive" evidence of leukemia on a marrow specimen but recovered, and later marrow studies were normal. Transverse bands of diminished density at the ends of the shafts of the long bones were demonstrated in 2 cases of bacteremia and they were indistinguishable from leukemic bands. If the cases of leukemia misdiagnosed as sepsis are added to the cases of sepsis (or severe infection) misdiagnosed as leukemia, the problem of differential diagnosis of the two diseases assumes proper proportions.

Sickle cell anemia, subacute bacterial endocarditis, lymphosarcoma and purpura were the other incorrect diagnoses considered more than once. In one case the question of leukemia was raised only after a sickling preparation of the patient's blood disproved the admission diagnosis. The development of signs of leukemia served to differentiate endocarditis and idiopathic purpura. Lymphosarcoma is less clearly differentiated from leukemia; it can be identified only by microscopic examination of excised tissue.

Other diagnoses considered when patients with undiagnosed leukemia were first seen were acrodynia, erythroblastic anemia, congenital hemolytic anemia, psychoneurosis, undulant fever and typhoid fever. An additional diagnosis worthy to be singled out was poliomyelitis. A four and a half year old boy had fever and pain in the legs, in August, 1946. Because of the time of the year and the finding of some spasm of the muscles of the lower extremities a provisional diagnosis of poliomyelitis was made. The blood count was normal; it is not known whether a lumbar puncture was done. The patient responded symptomatically to the Kenny treatment, but after two weeks a sharp rise in the total white blood cell count was noted and the child was admitted to Babies Hospital for study. Blood smears revealed many lymphoblasts, and roentgenograms of the lower extremities disclosed subperiosteal new bone formation in the fibulas. It is likely that the diagnostic roentgen changes could have been seen earlier.

A case similar to those with sepsis was

Fig. 9. Case iii, aged twenty-two months. Transverse bands of diminished density in agranulocytosis.

that of a three year old boy with primary tuberculosis and hematogenous dissemination in the spleen, liver, lungs and bone marrow. The clinical course and hematologic findings were compatible with leukemia and transverse bands were present in the long bones (Fig. 8). The correct diagnosis was made at necropsy. Several patients who were found to have aplastic anemia (Fig. 9) presented typical signs and symptoms of leukemia and were so considered until necropsy. The possibility remains that these patients had leukemia with complete "exhaustion" of the leukopoietic tissue.

From the roentgen standpoint, one must add metastatic neuroblastoma as a condition which may produce changes identical in every respect with those seen in the bones in leukemia. There was no clinical confusion found in the present series with regard to this disease but it is not an unlikely possibility. The case reported by Karelitz[29] illustrates the clinical similarity. Roentgen changes in a case of metastatic neuroblastoma are illustrated in Figure 10. Scurvy should cause no confusion as other signs of the disease should be evident by time the "Trümmerfeld" or the subperiosteal hematoma is observed (Fig. 11). Syphilitic periostitis can be differentiated by careful serologic and clinical study. Infantile cortical hyperostoses[6] and traumatic periostitis can easily be differentiated on the basis of history and the clinical blood picture. Baldridge and Awe[2] cited a patient with leukemia treated surgically for suspected osteomyelitis. Karshner,[31] too, reported similar clinical confusion. Repetition of this understandable error is to be expected and can be avoided only if other causes of bone pain and focal bone lesions are kept in mind.

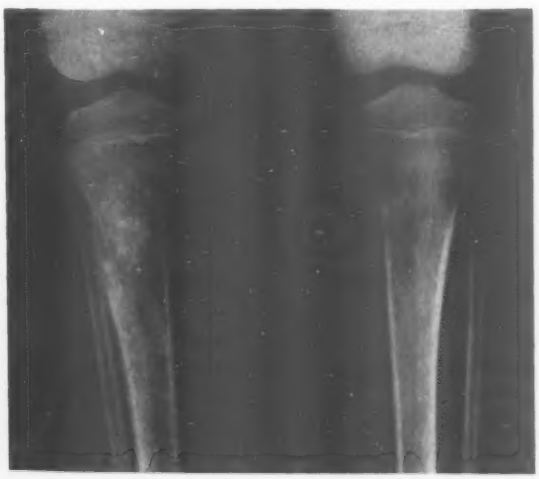


Fig. 10. Diffuse polyostotic destructive and productive lesions simulating leukemia in metastatic neuroblastoma.

Fig. 11. Characteristic "Trümmerfeld" of scurvy. Hemorrhagic tendencies and bone pain may accompany this picture.

Discussion.

The skeletal lesions and symptoms are less common in adults. The explanation most frequently offered for this has been that the marrow reserve in children is less than in adults. The adult possesses large amounts of fatty marrow which can be replaced by leukemic cells before osseous changes occur; the child, whose bones are completely filled with functioning red marrow, meets excess demands for medullary space by extramedullary hematopoiesis and by expansion of the marrow cavity.

The destructive and productive changes seen roentgenographically in the bones of children with leukemia represent variations in the response of the bones to the intraosseous proliferation of leukemic cells.

All bones are not equally affected, nor even all parts of the same bone. It is surprising, therefore, that the sternum has so often been selected for marrow aspiration regardless of the changes in other bones. It has already been pointed out that the irregular mineralization of the sternal ossification centers during infancy makes this site unsuitable from a technical standpoint. One infant in the present series had two unsuccessful attempts at sternal marrow aspiration before a tibial aspiration was performed. Moreover, it is possible that the sternum may be unaffected when there are gross lesions in other bones. In one of the cases proved by biopsy, marrow obtained by initial sternal aspiration was normal. A repeat examination several weeks later was characteristic of leukemia. The clinical success of the aspirations or biopsies suggests that correct diagnosis by this technique is more likely late in the disease when widespread proliferation of leukemic cells has taken place. Examination of the marrow is a valuable means of diagnosis in leukemia; the demonstration of roentgen lesions in the bones should assist in pointing out optimal sites for biopsy which should be preferable to blind sternal puncture.

The occurrence of abnormal (immature) leukocytes in abnormal numbers or in abnormal locations has been the most common feature in the cases studied. Early authors considered the bone changes primary and the alterations of the white blood cells secondary.[26,27,40] Neumann,[39] however, in 1878, formulated a concept which with slight modifications is applicable today in the consideration of the pathogenesis of this disease. He wrote,

> . . . certain facts, namely the appearance of significant splenic and lymph gland tumors without leukemia on the one hand, and the observation of leukemia without appreciable involvement of these organs on the other hand, can be reconciled satisfactorily if, through further investigations, the disease of the bone marrow can be established as the single constant finding in leukemia, in contrast to which the splenic and lymph node involvement has only an accidental significance.

Sabin[44] showed that if pigeons were starved, the cellular elements of the bone marrow rapidly became depleted and only three types of cells persisted. These were endothelial cells, fat cells (without fat), and reticulum cells. Regeneration of the marrow could be observed when feedings were resumed. Fat cells accumulated lipoid and assumed typical form with the nucleus flattened against the margin of the cell. Endothelial cells formed more endothelial cells and megaloblasts which gave rise only to the red blood cell series. White blood cells of all types were observed to develop from the reticulum cells, and only from the reticulum cells. Klemperer[33] reviewed the evidence in favor of assuming similar leukocyte origin in the human. Reticulum cells are not confined to the bone marrow but are practically ubiquitous in the human body though concentrated in the bone marrow, lymph nodes, spleen and liver. The clinical manifestations of leukemia depend on the abnormal proliferation of these reticulum cells; the sites of greatest normal concentration are those generally most markedly affected by malignant hyperplasia. Two additional factors are involved in the proliferation; one, an arrest in the maturation process and two, premature release of primitive cells into the peripheral circulation. In the "leukemic" type of the disease, the release factor is disturbed and the primitive cells enter the circulating blood; in the "aleukemic" type, the primitive cells are restricted to the sites of proliferation. The "leukemic" form naturally led to consideration of associated involvement of extramedullary sites as metastases from primary foci in the bone marrow. When the assembled evidence is reviewed, another explanation is obvious which fits more reasonably the variety of clinical features.

Malignant hyperplasia of reticulum cells occurs independently in one or several locations; and the clinical features depend on the degree of proliferation at the various sites. Leukemic proliferation may be marked in the tubular bones while the sternum is unaffected; cortical osteolytic lesions may result from proliferation of reticulum cells in the haversian canals rather than extension from foci in the medullary canal. Subperiosteal accumulations of leukemic cells need not necessarily represent extension either. Cases in which liver, spleen and kidneys are markedly involved may represent primary or even exclusive proliferation in these structures, and any structure may not show evidence of pathologic change early in the disease. The term leukemic "infiltration" used so frequently by pathologists, roentgenologists and clinicians alike has been avoided deliberately in this paper with the concept of multilocular primary foci of proliferation in mind. The concept is not a new one. Klemperer[33] favors consideration of this and allied diseases as diseases of the reticulum. Separation of cases into myeloid or lymphoid types is in many respects an example of overclassification. "Stem cell leukemia" represents a compromise with the urge to classify. Even separation of lymphosarcoma, and of leukosarcoma may be criticized from the standpoint of pathogenesis. Ehrlich and Forer[16] in the discussion of their case of leukemia associated with rheumatic fever write,

> The occurrence of subperiosteal elevation due to leukemic infiltration at a time when there was no enlargement of the liver, spleen or lymph nodes and no immature cells in the circulating blood would indicate that, coincident with the rheumatic infection there was not only an invasion of the circulating blood by immature cells, but also a generalization of the hematopoietic activity of the reticulum cells of the various organs, which, until that time was more or less localized to the periosteal elevation observed by roentgenographic examination and perhaps to other restricted foci in the body.

One case (Case II) in the present series in which extreme osteolysis was present was diagnosed as reticulum cell sarcoma on the basis of biopsy, and leukemia at necropsy. The former diagnosis in its most comprehensive form probably represents the more accurate histopathologic diagnosis. The term malignant reticulosis might be offered were not leukemia so firmly ingrained and true "leukemic" features so common. Consideration of this disease as a proliferative disturbance of the reticulum with manifestations dependent upon the loci of cellular accumulations relates the various clinical types to one another and to the pathologic changes observed in roentgen studies. Roentgen examination of the skeleton in children with suspected leukemia, or who suffer from an undiagnosed disease characterized by anemia, fever and pain in the extremities may offer confirmatory evidence in the first instance; and in either case may indicate the optimal site for tissue biopsy on which diagnosis may depend.

SUMMARY

Roentgen examination of the skeleton proved to be an aid in the diagnosis of leukemia in children. Our experience indicates that it should be more widely used.

The roentgen findings in the skeleton in 103 leukemic children are reported. The roentgen method was found especially valuable in the study of children who showed anemia, fever, and pain in the extremities. Conditions which simulate leukemia clinically and roentgenologically are discussed. The importance of the bone marrow as a primary site of proliferation of the leukemic cells is emphasized.

ILLUSTRATIVE CASES

Case I. Diagnosis first suggested by roentgen examination.

G.O'R. (BH No. 589591) was first seen in Vanderbilt Clinic at the age of two years and one month with the chief complaint of restlessness and pains in the legs of four months' duration. Family and past history did not contribute to the current illness.

The illness began with sudden pain in one ear associated with a temperature of 101°F., and

followed by myringotomy. Aural symptoms subsided in four days but were succeeded by pains in the lower extremities, localized to the hips, knees and ankles; these persisted to the time of admission to the clinic. Anorexia, irritability and fever accompanied the recurring exacerbations of the complaints. Local warmth but no swelling or redness was observed by the parents at the sites of pain. A month prior to admission to the clinic, the patient had been in another hospital for two weeks and had been treated with transfusion. A heart murmur which was said to have appeared during the course of the illness disappeared following transfusion.

Physical examination in the clinic revealed a well developed and well nourished boy who was warm, flushed, restless and uncomfortable. His temperature was 101.6°F. The positive physical findings included slight injection of the nasal mucous membranes, slight redness of the right tympanic membrane, and a "canker sore" on the internal surface of the right cheek. The tongue was coated, the pharynx reddened and the tonsils enlarged. A few cervical glands were palpated but no generalized glandular enlargement was discerned. The heart, lungs and abdomen were normal; liver, kidney and spleen were not palpated. The remainder of the examination also was normal. The impression was that the patient had rheumatic fever. He was given aspirin, and blood was obtained for a determination of the erythrocyte sedimentation rate, which was 85 mm. in one hour (normal 10–15 mm.). Two days later, the patient returned to the clinic; he had had one severe episode of pain in the left knee in the interim. The only new finding was a palpable liver, and he was admitted to the hospital for observation. Physical examination at this time revealed stiffness in the elbow and shoulder joints and a localized soft tissue infection in the left thigh. The diagnosis of rheumatoid arthritis was offered by the admitting physician.

In the following six weeks the diagnosis of acrodynia was suggested in addition to the previous diagnosis, but none could be satisfactorily confirmed. Attention focused on the nasopharynx so that one month after admission tonsillectomy and adenoidectomy were performed without complication but also without benefit. During this time the child ran a low grade fever. The erythrocyte sedimentation rate was consistently elevated. Repeated blood counts showed the hemoglobin to remain about 10 gm. per 100 cc. while the red blood cells numbered approximately 3,500,000 per cu. mm. White blood cells varied between 6,150 and 16,400 per cu. mm. with essentially normal differential counts. On two occasions blasts were noted but were considered consistent with the patient's supposed infection. Platelets were reported normal on smear.

After six weeks of observation the patient had a recurrence of severe bone and joint pain, and swelling of interphalangeal and ankle joints was observed for the first time. A mild generalized glandular enlargement became evident; the spleen was not palpable. Roentgenograms of the skeleton were made to evaluate these findings (Fig. 3). Dr. Caffey's report is quoted:

> Throughout the long bones there is an irregularity in density that is definitely pathological. All of the long bones show areas of diminished density of variable size and in the middle third of the right ulna there is a punched out area of diminished density which involves the entire shaft. There are broad bands of decreased density in the segments of all of the bones at the knees. Productive changes are seen which consist of diffuse cloaking of the shafts of the left humerus and right ulna. In the proximal thirds of both humeri, along the anterior margins, there are areas of diminished density. These are most clearly seen in the right humerus.
>
> In the skull there is a fine focal osteroporosis of the frontal and parietal bones.
>
> These findings resemble very much the changes seen in previous cases of lymphatic leukemia. They are so similar that they warrant a long continued observation before the diagnosis of lymphatic leukemia is abandoned. I believe that one can predict that if this patient survives for any length of time his skull will show large areas of destruction. One would also suspect that in disease with destructive changes of this extent and magnitude the concentrations of calcium and phosphorus in the serum will be changed, particularly increase in calcium. . . .

This totally unsuspected report led to an immediate marrow biopsy which was characteristic of leukemia and the child was discharged shortly thereafter and followed in the out-patient department until his death at home some five months later. During the first two months after the diagnosis had been made no great change was observed in the peripheral blood. A few blasts were seen on all counts but there was no leukocytosis, and platelet counts were normal. The last recorded count was taken three months after the diagnosis had been made and then there was a reduction in both platelets and red blood cells, and 18,850 white

blood cells with 16 per cent immature forms. The clinical course corresponded closely with the hematologic findings.

Case II. Extreme osteolysis in leukemia. B.H. (BH No. 435107) was a girl aged three years and one month when first seen at Babies Hospital. The family history and past history did not contribute to the present illness which began approximately ten weeks prior to admission. The patient had a severe vomiting episode which was thought to be related to food poisoning affecting several members of the household at the same time. Following several days of gastrointestinal symptoms the patient began to complain of severe pain, at first in her abdomen but later in her extremities. The pain was sufficiently severe to be unaffected by paregoric in therapeutic amounts. Gradually the child lost appetite and strength and after three weeks refused to walk. She was admitted to another hospital where she was found to have an elevated temperature and an injected pharynx. The tip of the spleen was palpable, the liver edge was felt 2 cm. below the costal margin. Laboratory studies there revealed a mild but progressive anemia and a leukopenia with several immature leukocytes. On one occasion normoblasts were noted in relatively high concentration. The blood smear was said to resemble erythroblastic anemia. Clinically the child's physical condition declined, weight loss and recurrent episodes of fever were noted and the child continued to complain of pains in the extremities. She was treated with two transfusions and after six weeks was transferred to Babies Hospital.

Physical examination at Babies Hospital revealed a sallow, irritable, emaciated child who cried whenever she was moved. Indefinite generalized tenderness was noted over the abdomen. The liver was palpated at the costal margin; the spleen and kidneys were not palpable. There was pain on touch in all the extremities which was interpreted as representing both bony and muscular tenderness. No joint changes were noted. Laboratory data revealed essentially normal blood counts for the first two weeks. However, occasional immature leukocytes were present on all examinations. Roentgenograms taken at the other hospital showed extensive destructive changes in the skeleton which had raised the question of hyperparathyroidism so that the inorganic content of the blood was studied on admission. Serum calcium was 12.6 mg. per 100 cc., serum inorganic phosphorus was 2.3 mg. per 100 cc. and the serum phosphatase was 5.4 Bodansky units. Hyperparathyroidism was thought to be unlikely, partly because of the low phosphatase; the moderate hypercalcemia was considered possibly to represent the result of overdosage with calcium gluconate and viosterol. Roentgenograms made at Babies Hospital after admission demonstrated extensive destruction of both cortex and spongiosa in almost all the bones (see Fig. 5). No productive changes were seen. The impression was reported as leukemia. The mediastinum was normal roentgenographically. Subsequent films revealed progression of the destructive changes and slight productive activity manifested by subperiosteal new bone formation. Pathologic fractures occurred in most of the long bones. Associated with these changes there occurred a depression of all the marrow elements, particularly the platelets; immature leukocytes became more frequent although the total white blood cell count dropped from an average of about 10,000 per cu. mm. to about 4,000 per cu. mm. Changes, surprising but not beyond understanding, took place in the inorganic components of the blood. The serum calcium climbed to unusual levels, registering 17.3 and 17.9 mg. per 100 cc. in a pair of duplicate determinations. The phosphorus at this time was 3.2 mg. per 100 cc. and the phosphatase 6.4 Bodansky units. At no time were Bence-Jones proteins found in the urine.

Considerable speculation took place concerning the diagnosis. Leukemia was opposed by some because of "the absence of lymphatic enlargement, palpable spleen and liver, and the return to normal of the blood count after transfusions." A biopsy was obtained from the lower end of the femur and was reported as "reticulum sarcoma of bone." Radiotherapy was given but the child contained to fail, developed an enlarged liver and spleen terminally and died after a total illness of five months. Necropsy showed leukemic proliferation in the liver, kidneys, colon, ovaries and bones, as well as other features characteristic of leukemia.

Case III. Agranulocytosis simulating leukemia.

L.S. (BH No. 363020) was admitted to Babies Hospital for the first time at the age of twenty-two months because of a recurrence of

agranulocytosis in the course of an upper respiratory infection. His first episode had taken place four months earlier associated with ulceration of the throat and gums, severe anemia and a leukopenia of 600 cells per cu. mm. with complete absence of granulocytes. Repeated transfusions and various types of supportive therapy carried the child through to apparent recovery in about two and a half weeks. Until the onset of the current upper respiratory infection the red blood cell counts were 3.2 to 4.7 million and the white blood cell counts were 4,500 to 7,800 per cu. mm. Polymorphonuclear leukocytes made up 18 to 38 per cent of the white blood cells. There was no history of exposure to poisons and the family and past history added no significant information.

The illness which brought the patient to the hospital began four days earlier with fever, sores about the mouth, mucopurulent rhinorrhea, cough, anorexia, restlessness and irritability. The liver was noted to enlarge rapidly and anemia and leukopenia supervened; polymorphonuclear leukocytes disappeared completely from the peripheral circulation.

On admission, there were signs of anemia and mild upper respiratory infection together with a scattering of "furuncles" on the skin. The cervical lymph nodes were the only ones palpable although both the liver and spleen were felt at the costal margin. The initial blood count was as follows: Hemoglobin, 8.5 gm. per 100 cc.; red blood cells, 2,552,000 per cu. mm.; white blood cells, 950 per cu. mm., polymorphonuclears 6 per cent, lymphocytes 88 per cent, monocytes 3 per cent, eosinophils 1 per cent, myeloblasts 2 per cent, platelets, 54,000 per cu. mm. Following a transfusion, a gradual recovery of all the cellular elements occurred although myeloblasts persisted in almost all counts. The only complication during the admission was the development of acute otitis media which cleared spontaneously. Roentgenograms of the long bones disclosed no abnormalities. The possibility of leukemia had not been excluded during this admission.

Two weeks after discharge from the hospital, the patient returned with fever, signs of upper respiratory infection and cervical lymph node enlargement. Examination at this time disclosed marked enlargement of the liver and spleen and enlarged inguinal and cervical lymph nodes. Several petechiae were noted and a tourniquet test was positive. The blood studies on admission revealed 91 per cent of the white blood cells to be lymphocytes and about 20 per cent of these were immature cells. Again there was some response to transfusion but because of recurrence of the otitis media and the condition of the nasopharynx, tonsillectomy was considered indicated and was performed as soon as the condition of the patient permitted. A temporary remission in symptoms followed this procedure and then the terminal episode of infection, neutropenia, splenic, hepatic and lymph node enlargement began and continued until death. A steady increase in the number of abnormal lymphocytes in the circulating blood accompanied this clinical picture. Roentgenograms of the long bones made during the second admission demonstrated focal areas of diminished density and transverse bands of diminished density at the ends of the shafts. These were considered as consistent with areas of leukemic destruction (see Fig. 9).

At necropsy, a diffuse and severe hypoplasia of the bone marrow was found. There was no evidence of leukemic proliferation in any of the organs.

CASE IV. Severe infection simulating leukemia.

L.F. (BH No. 586540) had been born prematurely at Sloane Hospital July 21, 1939, weighing 1,640 gm. The cause of the prematurity was unknown. He was discharged from the hospital after twenty-six days, weighing 2,480 gm., and showing no abnormalities. Jaundice had been noted on the fourth day and persisted until the eleventh day. Two blood counts while in the hospital had been normal. The patient was followed in Premature Clinic and progressed very well. Two days before admission at the age of three months he was brought to the clinic because his stools were green. At that time his liver and spleen were noted to be large. Blood count showed 68,000 platelets and 550 nucleated red blood cells per cu. mm. and 4 per cent of the leukocytes were blast cells. The enlargement of the liver and spleen had occurred since the last clinic visit approximately one month earlier when no such findings had been observed. Admission was advised for observation. On physical examination the infant weighed 9 pounds, 9 ounces and was well developed and moderately well nourished. The skin was pale;

several petechiae were observed on the scalp but none were seen elsewhere on the skin. Several were present on the hard palate. The pharynx was moderately injected. The spleen extended 4 cm. below the left costal margin and was firm and smooth. The liver was also firm and non-tender and extended 3 cm. below the right costal margin. The general opinion of the staff was that the infant had leukemia although the relationship of the findings to the nasopharyngeal infection and to the prematurity was not entirely clear. Sternal marrow punctures were attempted twice unsuccessfully and then marrow was obtained from one tibia. The presence of 35 per cent myeloblasts was interpreted as definite evidence of leukemia. The infant was discharged to be followed in the clinic. Very little change had occurred in several blood counts taken during the hospital stay although the initial thrombocytopenia did disappear. He was followed in the clinic and made an uneventful recovery in three months. About six months after discharge, he was readmitted with bronchopneumonia. He made an excellent recovery on sulfonamide. Advantage was taken of this second admission to obtain another marrow aspiration and this time the cell population was normal. He was last seen two and a half years after the second admission when he was normal in all respects.

Case v. Tuberculosis simulating leukemia. S.M. (BH No. 246125) was two and one-fourth years of age when admitted to the Babies Hospital because of cough since pertussis six months previously and a "tired feeling for three months." It was thought that there had been some evening temperature elevation for a month preceding admission.

On examination, the child appeared pale and chronically ill. The heart was slightly enlarged and a loud systolic murmur was heard over the precordium. The liver was felt 3 cm. below the costal margin; the spleen was 1 cm. below the left costal margin. The cervical lymph nodes were enlarged; many petechial hemorrhages were scattered over the skin. Physical signs indicated pathologic changes in the bases of both lungs, but this was not confirmed by roentgen examination. Blood examination revealed a severe anemia with leukopenia and almost constant presence of a few immature cells. Shortly after admission, ulcerating lesions were noted in the mouth and throat and a purulent otitis media occurred. The clinical picture improved with transfusion although the leukopenia persisted. It was thought that the infection was responsible for the blood picture and when the local lesions in the mouth had healed, the child was discharged. His tuberculin test had been negative.

Three and a half months after discharge, tonsillectomy was performed without complication. Three weeks later he was seen in clinic with a recurrence of anemia and thrombocytopenia; white blood cells numbered 21,800 per cu. mm., with 47 per cent neutrophilic myelocytes. Because of this the child was admitted for a transfusion. Examination at the second admission disclosed the child to be very pale. Moderate generalized glandular enlargement was present and several purpuric spots were noted. Many small cyst-like lesions were scattered over the skin. A soft systolic murmur was heard over the cardiac apex. The spleen filled the entire left side of the abdomen; the liver was tender and extended 3 cm. below the costal margin. A tourniquet test was positive. A transfusion was given with salutory effect and the child was considered to be suffering from leukemia. Roentgenograms of the long bones showed transverse bands of diminished density in the femurs (Fig. 8) and marked changes in both lungs consistent with bilateral suppurative pleurisy.

A dermatologic consultant thought that the skin lesions were similar to those seen in patients with tuberculosis. On the basis of this a tuberculin test, previously negative, was repeated and a strongly positive reaction was obtained. Scrapings from the skin lesions failed to demonstrate tubercle bacilli on smear or culture. During the next month and a half the patient had a slow but continuously retrogressive course and finally died. All blood counts taken during this period demonstrated a leukocytosis and none were free of immature leukocytes. The problem of diagnosis was still unanswered at the time of death.

Necropsy disclosed tuberculous pneumonia with hematogenous dissemination throughout all the viscera and bone marrow. Hyperplasia of the bone marrow was present and areas of myeloid proliferation were found in the spleen and liver.

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DISCUSSION

Dr. John Caffey, New York, N. Y. Reports on infant and juvenile leukemia of the skeleton have heretofore been limited to single case reports or a discussion of a small group of such patients. Dr. Silverman's findings, in contrast, report the study and correlation of an exceedingly large group of young leukemic patients. I want to re-emphasize his statement that the leukemic lesions in the skeleton are in no sense metastases but are the primary findings of the disease. Actually more than one-half of the reticulum tissue, from which leukemic cells originate, is found inside the bone in the bone marrow.

The diagnosis of leukemia in infants and children is often much more difficult than in adults because in children examination of the peripheral blood often does not provide the diagnosis; even when examinations are made over considerable periods of time. As Dr. Silverman indicated, there were normal numbers of white cells or reduced numbers of white cells in the blood of a substantial portion of his patients. These leukemic patients with chronic low grade fever, accelerated sedimentation rate of the erythrocytes, slight anemia, leukopenia, cardiac murmur and pain and tenderness and sometimes swellings in the extremities near the joints, simulate the clinical and hematologic pictures of rheumatic fever and rheumatoid arthritis. It is in this group that the demonstration of destructive and productive changes in the bones excludes rheumatic fever and rheumatoid arthritis and likewise directs attention to leukemia as the true disease.

It is probable that leukemic proliferations are present in the skeleton in all cases of leukemia and if all such patients live long enough they might all show roentgen changes. Leukemic tissues can be obtained from the marrow of the sternum by sternal puncture in almost 100 per cent of leukemic infants and children.

In my experience the only condition which resembles leukemia of the skeleton in roentgen examination is metastatic sympathicoblastoma. These two conditions usually cannot be differentiated conclusively from the roentgen findings alone but they usually can be differentiated on non-roentgen grounds. It is to be hoped that Dr. Silverman's study of a large group of leukemic infants and children will be repeated in other clinics where such material is available.

Dr. Paul C. Swenson, Philadelphia, Pa. I am sure that everyone will agree that the chief lesson to be learned from Dr. Silverman's most excellent presentation is that in the cases of disease of the hemopoietic system in infants and children the roentgenographic findings in the skeleton are generally more important than in the adult. Particularly is this true in the diagnosis of leukemia. In reading over Dr. Silver-

man's manuscript I was struck by the large percentage of cases in which there are roentgen findings quite out of proportion with the figures of other clinics. I was at once curious as to why comparable figures were not found elsewhere. For example, at Jefferson Hospital, where we have a most active and admirable hematologic service, investigation shows that although the number of cases seen in the same age period and over the same period of time is approximately the same, there just has not been any roentgen survey of the skeleton done. It has been neglected apparently because it has not been considered a necessary and important diagnostic help. Only about one-half of Dr. Silverman's cases showed bone pain, yet surveys were nevertheless made. Moreover, our hematologists and pediatricians have presumably not paid enough attention to the finding of bone pain. With the case which Dr. Silverman cited (Kalayjian, *et al.*) there have been but 4 cases of proved leukemic bone involvement in children in our hospital records during the past four years. Now having heard Dr. Silverman's paper, we should all be stimulated to do a more thorough work-up, surveying the skeleton of all infants and children where there is a question of some disease of the hemopoietic system. Only by searching for the unexpected is an occasional rare case discovered and new knowledge gained.

However much one may agree with the thesis of Dr. Silverman in regard to reticulosis and the apparent close relationship between reticulum cell sarcoma, Hodgkin's disease and leukemia, one must perhaps proceed with caution in making too much of a sweeping factual statement before more is known about this phase of the problem. All evidence points to their close relationship, it is true. Six cases were recently studied in the Pathology Department at Jefferson Hospital by Dr. Herbut, Miller and Erf where a biopsy of three different lymph nodes from three different regions at postmortem showed three different histopathologic structures—Hodgkin's disease, reticulum cell sarcoma, and lymphosarcoma. We all know the frequency with which a lymphosarcoma may suddenly become acute leukemia, again emphasizing the close relationship. However, we still have not discovered the x factor that brings about this transformation or differentiation and until we know that, for purposes of classification I think leukemia must still remain leukemia and sarcoma under its old category although all evidence seems to point to the fact that Dr. Silverman's thesis is correct. There is just as much reason, it seems to me, to theorize about a basic malignant reticulum cell as there is to assume that there is a basic malignant mesoblast as a stem cell for all osteogenic sarcomas.

We feel that Dr. Silverman has made a very important contribution to the understanding and the diagnosis of leukemia by emphasizing the importance of the use of the roentgen findings.

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THE SIGNIFICANCE OF TRIANGULAR HILAR SHADOWS IN ROENTGENOGRAMS OF INFANTS AND CHILDREN*

By ROLFE M. HARVEY, M.D., *and* RALPH S. BROMER, M.D.
BRYN MAWR, PENNSYLVANIA

A TRIANGULAR shadow of increased density is seen occasionally in roentgenograms of infants, less often in younger children, projecting from the region of the hilum of the right lung, less frequently from the left. This shadow has a sharp lateral margin which ends in an inferior angle, usually less than 90 degrees and is either in close relation to, or merges with the interlobar fissure marking. It is rarely found simultaneously on both sides. The density in the lateral view is located in the anterior mediastinal space (Fig. 1).

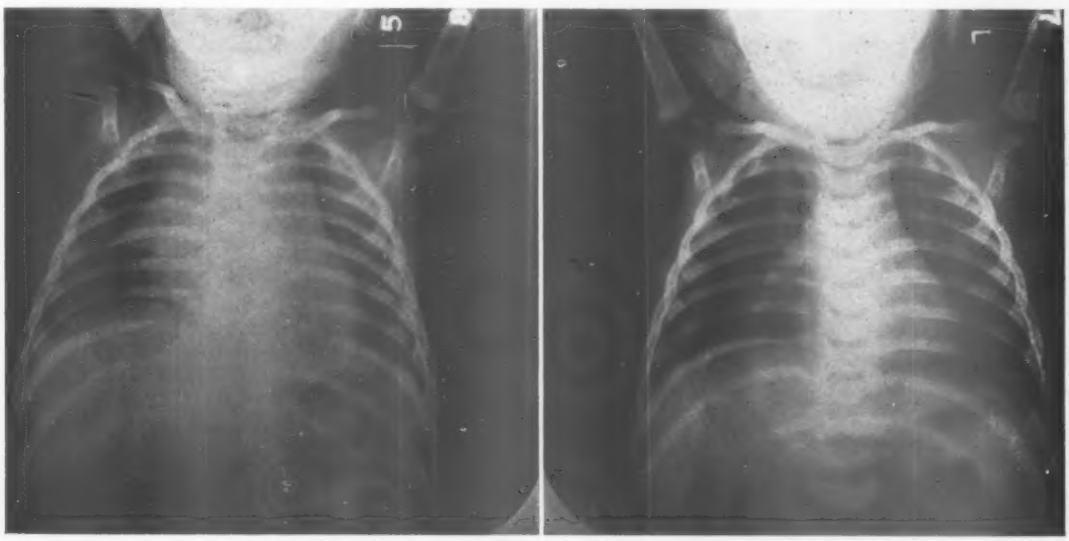

FIG. 1. Inspiration and expiration roentgenograms of chest of six months old child admitted with diagnosis of otitis media. These show typical triangular shadow projecting to right of superior mediastinum and blending with cardiac shadow. Old tuberculin reaction negative.

Some of the suggested causes of this shadow are thymic enlargement, tumors of the thymus, enlarged mediastinal and hilar lymphatic nodes, partial atelectasis of either upper lobe and consolidation along the mesial margin of either upper lobe. R. A. Harvey[5] called attention to the role of this shadow in the diagnosis of mediastinal pleurisy. Comparatively little attention has been paid to this condition in the American and English literature. With the publication of Harvey's article, interest in the condition became more general. It seems that in some instances undue emphasis has resulted and diagnoses of mediastinal pleuritis have been made without sufficient justification. In an effort to clarify the diagnosis a series of 300 consecutive examinations of the chest were studied at the Children's Hospital.

MEDIASTINAL PLEURITIS

Reyher[8] was apparently the first to re-

* From the Department of Roentgenology, Children's Hospital of Philadelphia. Presented at the Forty-eighth Annual Meeting, American Roentgen Ray Society, Atlantic City, N. J., Sept. 16–19, 1947.

late this characteristic shadow to pleuritis of the anterior mediastinum in the anterior superior mediastinal space. Saupe,[10] in reporting his cases, gave no autopsy findings. Engel and Schall[3] devoted considerable space in their textbook to a discussion of the condition and of the characteristic roentgen findings. Gefferth[4] reported a case of a patient, seized with a high fever, who had physical signs in the region of the inferior angle of the right scapula. In the roentgenogram, the typical shadow was found in each hilar area. In the cases reported in the German literature, emphasis is laid upon the possible long duration of the shadow, in Engel's case[2] for one and a half years. This was not regarded as an argument against the diagnosis of mediastinal pleurisy. R. A. Harvey[5] reported 8 cases of anterior mediastinal pleurisy with however only 1 case verified by autopsy findings. The roentgenograms of 5 of the patients showed the characteristic shadow with sharply defined lateral border and the sharp inferior angle which the German writers considered typical of pleuritis of the anterior superior mediastinum. Harvey quoted Pincherle[6] who reported 30 instances in 2,000 routine examinations of the chest in young children, an incidence of 1.5 per cent. He stated that clinically there is no single symptom or group of symptoms that permit a definite diagnosis of mediastinal pleurisy, even with effusion, without a roentgenogram of the chest. The cases are usually of pneumonic origin. He also considered that one of the more typical findings is the sharp lateral margin of the shadow, ending in an inferior angle usually less than 90 degrees and in relation with or near the interlobar fissure. He emphasized that proper positioning of the patient on the film must be maintained, as slight rotation of the patient may obscure the lateral borders of the mediastinal shadow. Low position of the tube accentuates the angular deformities and residual pleural thickening in cases of mediastinal pleuritis may cast a solid triangular shadow from this projection. Correct alignment in 2 of his cases in which this occurred showed only linear shadows representing thickened pleura in the central lobar fissure area. This thickening was a residual characteristic of all of the cases which cleared of their major density during the period of observation.

The mediastinal space is divided usually into four major subdivisions (Caffey).[1] The space, as a whole, is bounded laterally by the pleuras which are continuous with the costal and diaphragmatic pleuras, the sternum in front and the vertebrae behind. In the superior mediastinum, the lower boundary of which is a line drawn from the fourth intervertebral disc to the junction of the manubrium and body of the sternum, are located the superior portions of the thymus, the aortic arch and great vessels with their branches and some tracheal lymphatic nodes. It is traversed from above downward by the trachea, the thoracic duct, and the vagus, phrenic and sympathetic nerves. It is the anterior portion of the superior mediastinum in which the shadow appears in the lateral view.

Below the superior mediastinum are the three other subdivisions, the anterior, the middle and the posterior. The anterior mediastinum is a shallow space between the sternum and the pericardium and contains the inferior portions of the thymus and a loose areolar tissue in which a few lymph nodes are embedded. It is in this space that an effusion may cast a triangular shadow with the base on the diaphragm and with a convex hypotenuse form which can be mistaken for an area of atelectasis either in the right or left lung or for enlargement of the lower thymic segments. The middle mediastinum contains the pericardial sac with the heart enclosed and some tracheal and tracheobronchial lymphatic nodes. The posterior mediastinum is the largest of the four subdivisions and is bounded by the vertebral column posteriorly and the pericardium anteriorly. It contains the esophagus, the thoracic duct, the descending aorta, inferior vena cava, phrenicopericardial ligaments, azygos vein and the sympathetic nerves.

In the roentgenogram the anterior medi-

astinum is the clear triangular space between the sternum and the anterior border of the heart. The superior mediastinum is divided by the shadow of the trachea and the posterior portion is not clearly defined due to the superimposed shadows of the scapulas.

In a pleuritis or effusion all subdivisions may be affected simultaneously or they may be involved singly. Triangular shadows result in the roentgenogram when the anterior mediastinum, inferior portion, is affected. In these the base rests on the diaphragm. When the superior portion of the anterior mediastinum is affected the triangular shadow, regarded by German writers as typical, results. The pleura on each lateral margin of the mediastinum is reflected into the small fissures located on the mesial surfaces of the lungs and the involvement of these fissures by effusion may be the cause of the shadow. Prolongations into the small interlobar fissure on the right side may cast transverse linear shadows which are an aid in the differential diagnosis of pleural exudate from the right lobe of the thymus (Engel and Schall[3]) (Caffey[1]). Triangular-shaped shadows with the apex pointing away from the hilum toward the periphery of the lung may also result.

Fig. 2. Roentgenogram to illustrate occurrence of triangular shadow to the left side of the mediastinum. Six months old child admitted with upper respiratory infection, subsiding in one week. Old tuberculin reaction negative. Clinical recovery in one week. Film four months later showed no evidence of any abnormality.

In the series of 300 consecutive examinations of the chest studied at the Children's Hospital 9 cases were found showing the typical triangular hilar shadow. Of the 9, none were seriously ill nor had they any

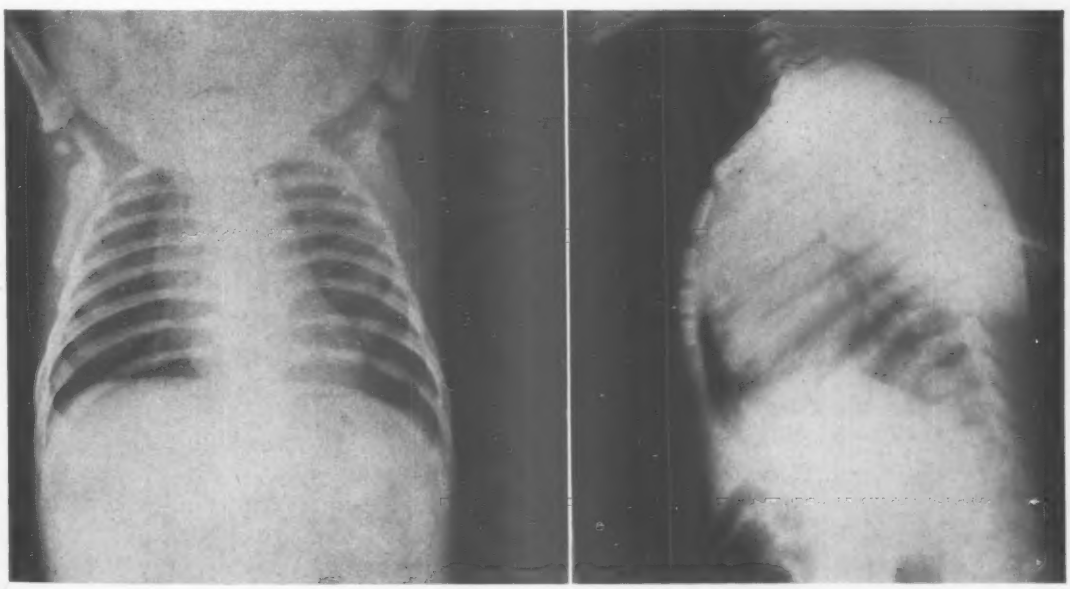

Fig. 3. Roentgenograms of three months old infant referred for possible thymus. These show location in anterior mediastinum in lateral view and more usual rounded appearance of the thymus gland.

history of previous serious respiratory illness. Almost all of the patients were referred for examination from the Out-Patient Department. None required hospitalization. In only 1 case was the shadow found on the left side (Fig. 2) and no bilateral cases were encountered. The ages of the patients ranged from three weeks to twenty-three months. Seven of the 9 cases were less than one year of age. In 6 of the 9, the shadow could be located definitely in the anterior mediastinum in the lateral view (Fig. 3). In the other 3 cases, localization in the lateral view could not be determined accurately. More recently 2 cases (not included in the series studied) were found, both in infants who were not ill and had never had any serious illnesses. Ryle[9] stated that in a study of over 500 well babies from all economic levels he found an incidence of this triangular shadow in 3 per cent and believed it was due to persistence

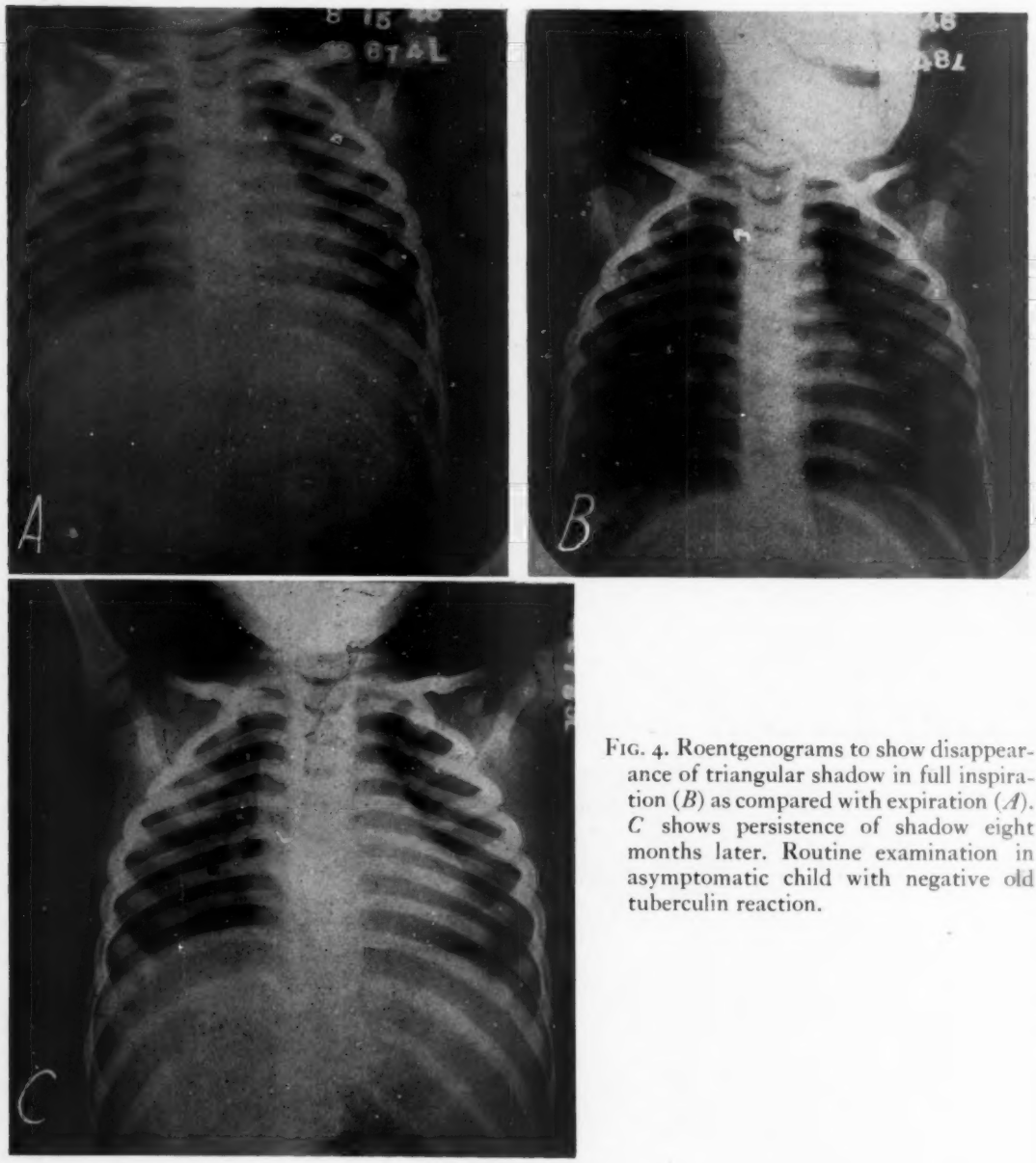

FIG. 4. Roentgenograms to show disappearance of triangular shadow in full inspiration (*B*) as compared with expiration (*A*). *C* shows persistence of shadow eight months later. Routine examination in asymptomatic child with negative old tuberculin reaction.

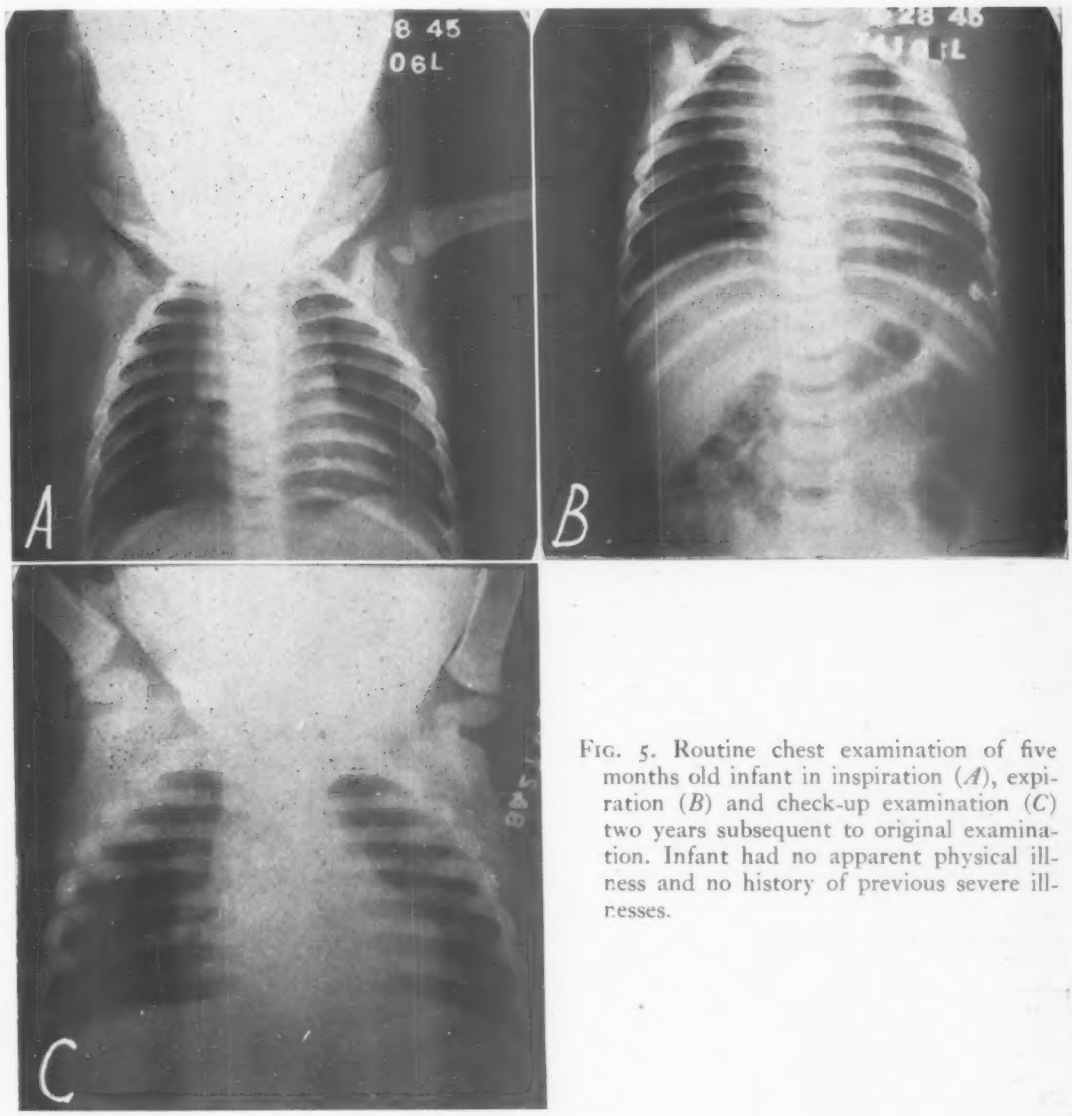

Fig. 5. Routine chest examination of five months old infant in inspiration (*A*), expiration (*B*) and check-up examination (*C*) two years subsequent to original examination. Infant had no apparent physical illness and no history of previous severe illnesses.

of the thymus. The same percentage incidence was found in the series reported in this article.

THYMIC ENLARGEMENT

It is impossible to prove conclusively from personal observation the definite cause of the shadow inasmuch as it has never been encountered in children who were so seriously ill that death resulted and an autopsy was obtained. In the 1 case reported by Harvey,[5] in which an autopsy was obtained, mediastinal adhesions were found and in the roentgenogram as reproduced, the sharply angulated lower border was not pronounced.

From the study of the cases of this series the causes for the belief that the shadow is most often due to persistence of the thymus are as follows:

1. The occurrence of the shadow in healthy infants in whom no previous serious respiratory illness has occurred.
2. The frequency of the finding in routine chest examination.
3. The fact that Wasson[11] has demonstrated in his studies that the thymus can cast a sharply angulated shadow.
4. The persistence of the shadow for long

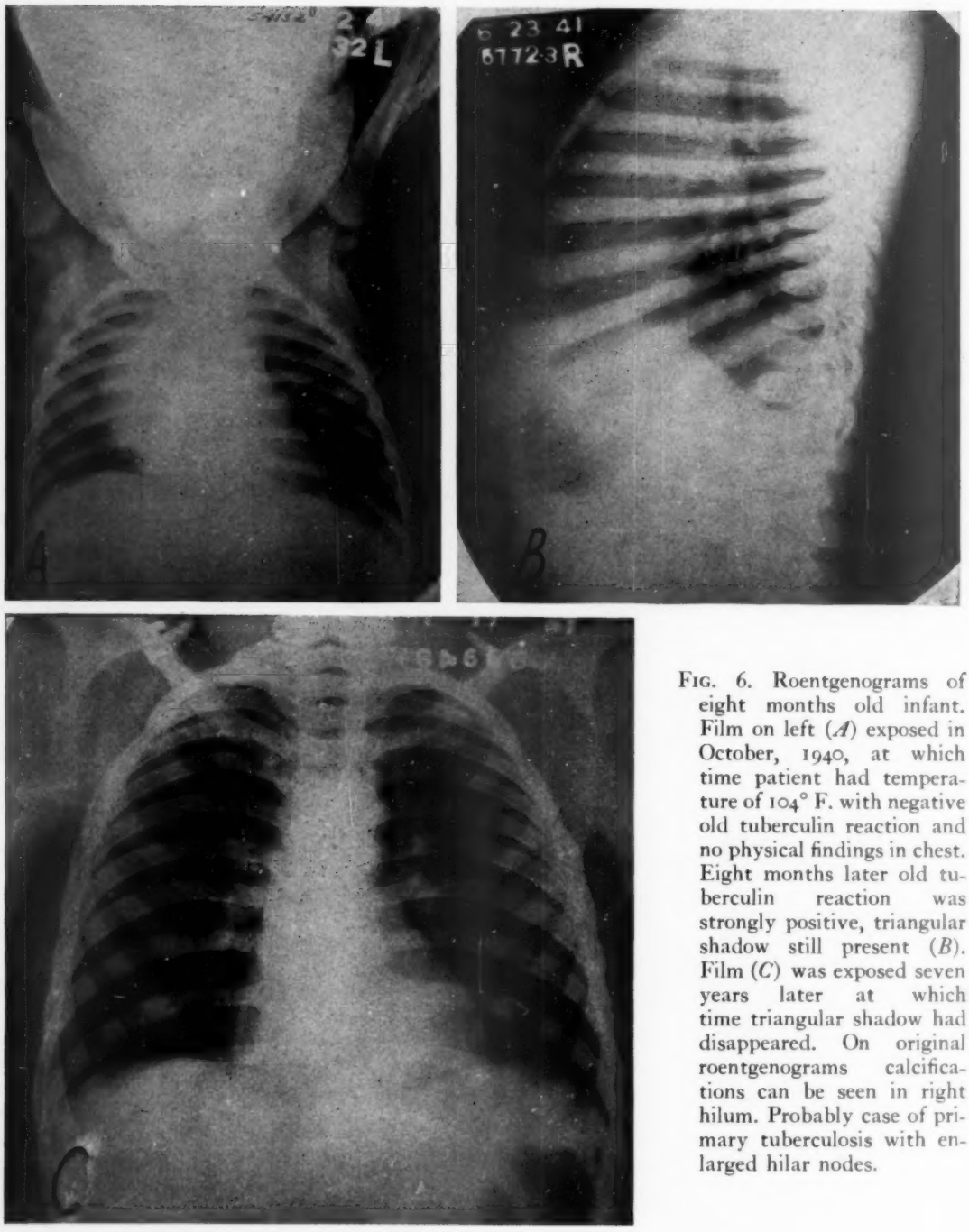

FIG. 6. Roentgenograms of eight months old infant. Film on left (*A*) exposed in October, 1940, at which time patient had temperature of 104° F. with negative old tuberculin reaction and no physical findings in chest. Eight months later old tuberculin reaction was strongly positive, triangular shadow still present (*B*). Film (*C*) was exposed seven years later at which time triangular shadow had disappeared. On original roentgenograms calcifications can be seen in right hilum. Probably case of primary tuberculosis with enlarged hilar nodes.

periods of time in otherwise healthy infants. If the shadow were due to mediastinal pleurisy for similar long periods it would seem that effusions would no longer be present and that adhesions alone could not produce such a shadow (Fig. 4).

5. The fact that often the lower border of the shadow is not definitely located at the interlobar fissure and that as a rule no transverse linear shadows can be seen.
6. The shadow is not confined to any anatomical unit of the lung.
7. The age incidence, predominantly the first year of life.

Thymic tumors usually cast larger and

wider shadows and should not cause much difficulty in differential diagnosis. Other points of differential diagnosis in favor of thymic enlargement, quoted by Harvey,[5] are rounded corners of thymic shadows, more often bilateral involvement, the disputed question of tracheal and esophageal deviation supposedly due to the enlarged thymus, and decrease in size following roentgen therapy. However, in the cases observed in this series there were no clinical indications for roentgen therapy and the other roentgen signs quoted were not found (Fig. 5).

ENLARGED TUBERCULOUS HILAR NODES

In all but 2 of the 9 cases found in this series the old tuberculin reaction was negative. This argues against a diagnosis of tuberculosis as a cause of the shadow. In some cases noted previous to the beginning of the collection of this series, which were observed over long periods of time, no calcifications developed. The long straight or slightly convex lateral border of the shadow is difficult to reconcile with the appearance of a mass of enlarged nodes. However, Redeker[7] has observed a typical, angulated shadow in the roentgenograms of a patient who was later proved at autopsy to have a mass of enlarged nodes which accounted for the triangular shadow in the roentgenogram (Fig. 6).

PARTIAL ATELECTASIS OF THE RIGHT UPPER LOBE

The principal argument against the diagnosis of partial atelectasis as a cause of the shadow under discussion is the lack of evidence of upward retraction of the short fissure which usually occurs as the atelectatic portion of the lung folds like a fan toward the mediastinum. This did not occur in any of the 9 cases of the series. A second argument against this explanation is the extension of the shadow below the short fissure in many cases. This would not occur in atelectasis of any portion of the right upper lobe.

CONSOLIDATION ALONG THE MESIAL MARGIN OF THE UPPER LOBES

Caffey[1] has suggested that consolidation along the mesial margin of the right upper lobe could produce the shadow. The previous good health of the majority of cases, the frequency of the finding, the persistence of the shadow and the lack of a history suggestive of pneumonia would tend to rule out this diagnosis in the cases of this series.

SUMMARY

A triangular shadow projecting commonly from the right, less often from the left hilum in the superior mediastinum was found in 9 patients of a series of 300 consecutive examinations of the chest of infants. Possible explanations of the cause of this shadow are discussed and reasons given for attributing it in the large majority of instances to persistence of the thymus. Absolute proof cannot be obtained because of lack of autopsy examinations. In comparatively rare instances it can be due to pleuritis of the superior portion of the anterior mediastinum. If a history of pneumonia can be obtained the possibility of consolidation of the mesial border of the right upper lobe must be considered. Atelectasis is more difficult to confirm as a diagnosis. Enlarged tuberculous nodes seem to be a still more remote possibility.

In regard to prognosis, the fact that in all cases which have been followed for several years no serious consequences have developed, is emphasized. The shadow eventually disappears. Only after a careful evaluation of the clinical findings and history is a diagnosis of pleural involvement of the superior mediastinum warranted.

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DISCUSSION

DR. JOHN CAFFEY, New York, N.Y. I am sure that we all have seen numerous examples of triangular shadows at the pulmonary roots which Drs. Harvey and Bromer have described so well. These shadows remain a great puzzle to me because they are seen in both symptomatic and asymptomatic patients; and we rarely prove their cause or demonstrate the anatomical structure which casts them. Certainly there must be many causes of these shadows; the most common in my opinion is the right lobe of the thymus. Other triangular lesions at or near the hilum such as pneumonic consolidation and atelectatic pulmonary segments, and loculations of pleural exudate can also all cast triangular shadows. On the right side the presence of a "pleural line" in the small pleural fissure helps to confirm the presence of pleural exudate.

Recently I saw a patient in which a bronchogenic cyst projected beyond the hilum and caused a triangular shadow. The authors are to be commended for their study of a common and baffling shadow which is seen in both sick and healthy patients.

DR. GEORGE W. GRIER, Pittsburgh, Pa. I did not come here prepared to speak on this subject, so I hope you will excuse this extemporaneous discussion, but this is a subject in which I have been interested for many years, twenty or twenty-five at least. When I first saw these things, I thought, of course, that they were an unusual type of enlarged thymus, and I think in some of my earlier writings on enlarged thymus I described this as one of the different shapes.

And then I ran into a series of cases that did not respond to the usual treatment for thymus, and I finally became convinced that they could not be due to thymus because these cases went on for two or three years, as has been mentioned. I actually taught medical students for a number of years that these shadows were congenital in origin and probably were due to congenital atelectasis.

I remember within the last two or three years I have run into 2 or 3 cases at the Children's Hospital, children acutely ill with upper respiratory infections, that showed these shadows and within two or three weeks re-examination showed them to be gone. So, I feel pretty sure that there are at least three different causes for this shadow. Of course, if you treat them for enlarged thymus and it does not go away, I think that would rule thymus out. In acute cases, probably re-examination would rule out mediastinal pleurisy. The third—the anomalies—I don't know how to rule that out.

DR. EDWARD B. D. NEUHAUSER, Boston, Mass. I think the paper by Drs. Harvey and Bromer is an extremely important one. We, too, have been interested in this shadow, as I am sure has everyone else who sees many films of children. I have been worried about some of the discussion, and some of the remarks that have been made. I do not like to carry out a crusade, but I hate to hear given forth at any large meeting words like "hypertrophy of the thymus," "persistent thymus," "X-ray treatment of the thymus."

It seems to me the significance of this shadow is that in about 99 per cent of the patients it is of no importance whatsoever, and very often the radiologist, by reporting shadows, giving very lucid descriptions of shadows, can lead the pediatrician, the referring physician, far astray so that he gets worried; he sends the patient in for roentgen therapy; it costs the patient a great deal of money; the family is all excited, and all to no avail whatsoever.

It is certainly my feeling that we should in our own minds form an opinion as to whether this shadow is of any significance in that particular patient. If we feel it is of no significance, I am not at all sure that it should be reported as a large triangular shadow projecting out from the right side. It should be recognized as a portion of the picture of the healthy chest. I certainly have had a great deal of trouble with families where this has been reported as abnormal and they cannot be convinced for the next few years that they have a well child.

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TUBERCULOUS CALCIFICATION

A CLINICAL AND EXPERIMENTAL STUDY*

By ROBERT G. BLOCH, M.D.

CHICAGO, ILLINOIS

OF THE three healing processes of tuberculosis—resorption, fibrosis and calcification—the importance of the last has often been denied. The majority of pathologists look upon the deposition of calcium in necrotic tuberculous areas as an after effect to an already accomplished healing of the lesion. Jaquerod,[7] in a book devoted exclusively to the study of healing changes in tuberculosis, wrote, "the importance of this process in the healing of pulmonary tuberculosis has been considerably exaggerated. . . . In reality this process has only an insignificant influence in the cure of evolutive tubercular lesions." He continues with a startling argument, "generally no traces of calcification are found in the radiographs of cured tuberculous patients. . . . This process has therefore no curative value." Wells and Long[11] expressed their opinion that " . . . we have no evidence that calcification favors the healing rather than follows the healing. . . . " One of my teachers in pathology used to express the prevailing opinion by explaining that "calcification is the tombstone which nature erects on the grave of a dead tuberculous lesion." Space does not permit a detailed discussion of the healing by resorption and fibrosis; complete resorption cannot be considered as established after the disappearance of all pathologic shadows from the roentgenogram and, indeed, not even negative findings on macroscopic postmortem examination justify the assumption that all traces of tuberculosis have disappeared. Fibrosis, in the view of many clinicians, represents a transformation of the whole tuberculous involvement into scar tissue; it is more correct to look upon it as a perifocal tissue response, regardless of how powerful and overwhelming in size the fibrous reaction may be as compared with the exciting but persisting caseous focus. With some reserve, but certainly grossly and roentgenologically speaking, fibrosis should be looked upon as a clinical-pathological healing if it is powerful enough to permanently confine necrotic residuals (Fig. 1) and to prevent bacilli harbored within them from escaping into the neighboring parenchyma or into the bronchial system.

FIG. 1. Photomicrograph of fibrocaseous tuberculous focus. Multiple small areas of necrosis are densely encased by fibrosis.

* From the Department of Medicine, University of Chicago, Chicago, Illinois. Presented in part at the Joint Meeting of the American Roentgen Ray Society and the Radiological Society of North America, Chicago, Ill., Sept. 24–29, 1944.

Complete calcification, that is the deposition of calcium salts, essentially of calcium phosphate, in a caseous area leading to its calcareousness or petrification, occasionally even to ossification, is the most reliable and the only irreversible healing process of the caseous tuberculous lesion itself. This is the clinical and roentgenologic experience. The question might be asked why caseation, the prerequisite for calcification, should be stressed so much in a discussion of the healing processes since not all tuberculous lesions undergo caseation. The answer is that non-caseating tuberculosis heals comparatively easily; that caseation takes place in the overwhelming number of even smaller involvements; that it is the forerunner of excavation or rather that a caseous lesion indeed *is* a cavity without bronchial communication which may establish itself at any time. Since the cavity is the ever threatening redistributor of the disease to other parts of the lung, the importance of the conversion of necrosis into calcification cannot be doubted. If any of the tissue changes observed in tuberculosis can dispel the doubt expressed by Pagel[8,10] and others that the healing of tuberculous foci in any case is not absolute but only relative, it is the complete transformation of a caseous area into a calcareous mass.

In recent years impetus has been added to the study of calcified lesions through their importance in the epidemiology of tuberculosis. In previous writings I have pointed out [2,3] that the differentiation between the residuals of childhood or primary infection and small calcified foci resulting from reinfection is impossible and that many of the so-called Ghon's tubercles found in adults are the final product of the adult type of tuberculosis. This, together with the fact that the reinfection type lesion is now recognized as the major problem in the clinical and public health aspects of tuberculosis, further enhances the importance of calcification.

In part, at least, the significance of calcification has been underestimated because of observations that incrustation with calcium salts is a frequent and possibly insignificant by-product of non-tuberculous

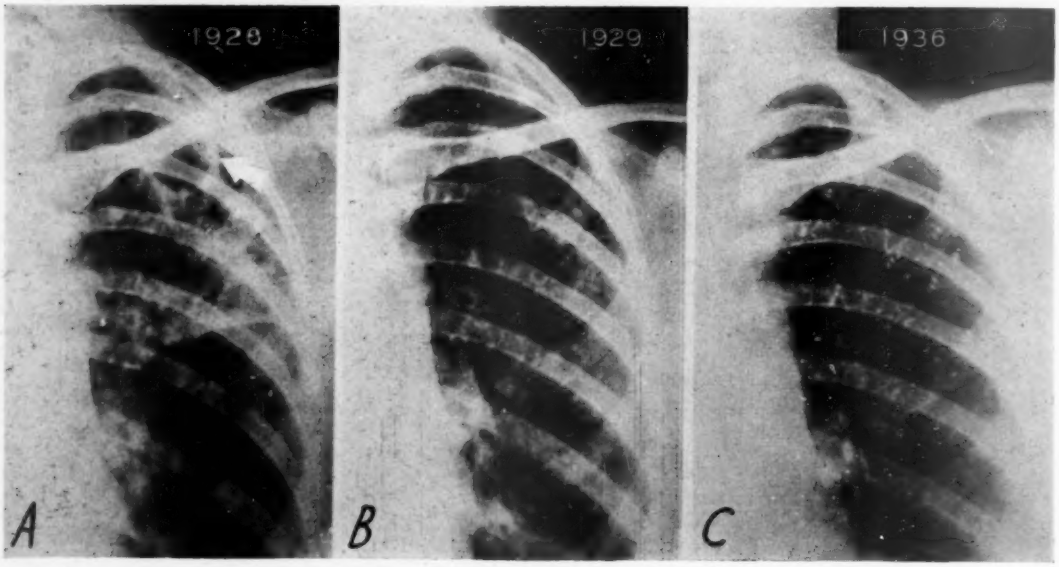

FIG. 2. *A*, diffuse exudative-caseous tuberculosis with large subapical cavity in 1928. *B*, after one year resorption of exudation and spontaneous closure of cavity, scattering of small residual caseous lesions. *C*, after eight years numerous minimal calcified foci, many of them not in view during the non-calcified stage in *B*. Patient clinically well since 1929.

involvements, such as other infections, tumors and foreign bodies; the incidental occurrence in these cannot diminish the importance and the curative value of calcium deposition in tuberculous necrosis. No favorable end result in the treatment of adult pulmonary tuberculosis inspires me with as much confidence in its stability as the appearance in the roentgenogram of the dense opacities which promise solid calcification.

No proof has been offered for the contention[8] that calcium salts can be resorbed after once having led to petrification and, in this fashion, can cause reactivation of the disease process. Several investigators[5,9] have disproved the persistence of viable tubercle bacilli in minimal calcareous residuals of primary infection in the lung parenchyma; there is no reason to assume that their findings do not apply to equally small residuals of reinfection tuberculosis.

Another reason for the erroneous concept of the significance of calcification seems to have been due to the exclusive appraisal of pathologic changes by postmortem examination. Studies by autopsy capture the status of tuberculosis only at the time of death. They leave the question of the sequence and timing of pathologic changes to mere speculation. Their value is richly enhanced by the revealing studies which can be made by serial roentgenologic examinations, the sole means of investigation which allows for the element of time. It is of paramount importance in the study of a disease which can extend through decades of an individual life.

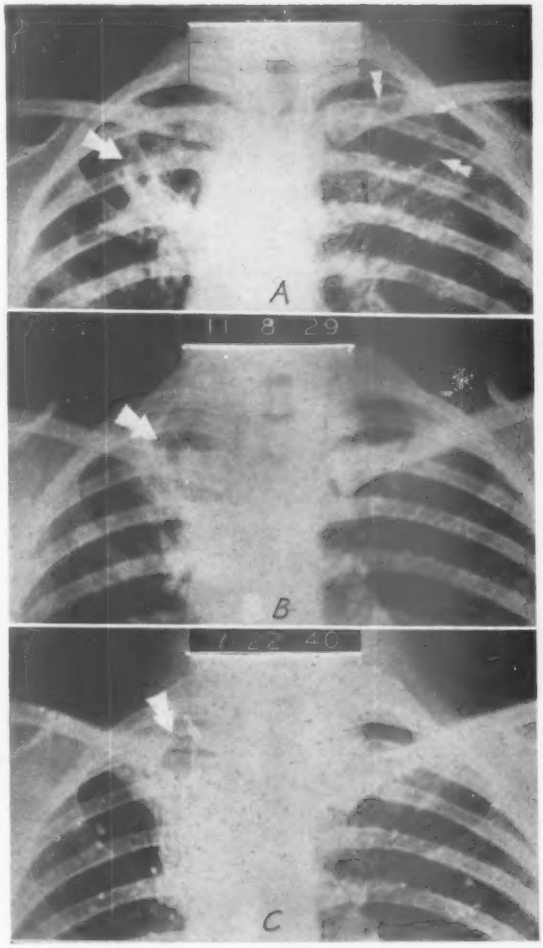

Fig. 3. *A*, fibrocaseous tuberculosis with subapical cavity in the left lung, fresh exudative involvement in the lower part of the left upper lobe and in the right upper lobe where it includes a large over-inflated cavity. *B*, after three years fibroid retraction of the left cavernous area into the apex. Suggestion of persistence of right subapical exudation, small residual cavernous lesions in both subapical areas. *C*, after fourteen years persistence of enlarged left apical cavity, seeming disappearance of right subapical cavity, dense calcification of metastatic lesions in both subapical areas. Sputum strongly positive. Patient admitted for surgical collapse.

CLINICAL-ROENTGENOLOGIC OBSERVATIONS

The average minimal period during which adult reinfection tuberculosis can change from the active exudative-caseous state to complete healing by calcification is six to eight years (Fig. 2), two to three times as long as in the primary infection focus of the child. Small caseous lesions, especially the metastatic foci which originate from pre-existing excavations through bronchogenic aspiration of bacilli, calcify more easily. This is especially the case after distribution by blood during pulmonary hemorrhage. Such lesions may be too small to register roentgenologically in the non-calcified state and become visible only with progressive calcification. The end result frequently is the picture of a well calcified, widely scattered tuberculosis in which, however, the original cavernous le-

sion remains, requiring closure by lung collapse (Fig. 3).

The development of extensive fibrosis often leads to the roentgenologic diagnosis of complete healing (Fig. 4). In such cases it is not possible to discern the already mentioned caseous foci which may persist as nuclei of the fibrous areas. They will come into view in later years when calcium has been deposited in sufficient quantity, signifying that the previous state had been one of latency rather than of healing. Even after the appearance of a considerable degree of calcification it is indicated to cautiously term such involvements calcio-caseous-fibroid tuberculosis. This avoids the diagnosis of irreversibly healed disease until it has been substantiated by several more years of roentgen observation. Incrustation and resorption of caseous material can continue after very extensive calcification has already occurred (Fig. 3).

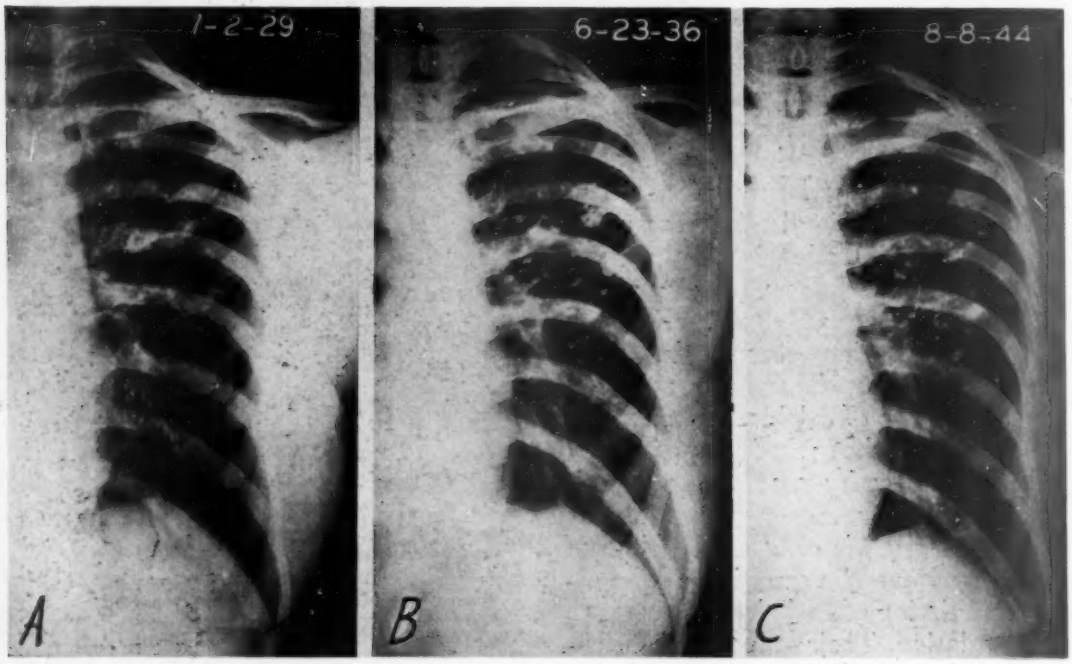

FIG. 4. *A*, well fibrosed upper lobe tuberculosis. Patient clinically well. *B*, after seven years heavy calcium deposits within the fibroid areas. *C*, after fifteen years further absorption from calcio-caseous areas leaving them smaller and denser. No further roentgenographic changes since.

The roentgenologic aspects of calcified lesions require a clarification of the term, "calcification." Clinical usage through the years had led us to speak of a calcified focus when we find an opacity of a certain size, outline, location and especially of great density in the lung field. This empirical appraisal is justified if the name "calcification" is used for any lesions containing sufficient calcium to be recognized as such on roentgen observation, regardless of their consistency and other pathologic properties. The term is incorrect if, as is mostly the case, a calcified lesion is assumed to be a solid rock-like focus which Ghon and others have called "petrified." A focus may contain an abundance of calcium deposits and yet remain soft and caseous or chalky, occasionally harboring viable organisms. If communication with the bronchial system occurs, excavation will, and distribution of new involvement may, result. This interplay between caseation and excavation cannot be expected to end until the original lesion has changed into an almost solidly calcareous mass. In the larger lesions of more than 1

cm. in diameter this is a comparatively rare occurrence; only small and especially minimal lesions of great homogeneous roentgenographic density can be assumed to be securely petrified. The interplay between caseation, calcium deposition and late excavation occurred in a lesion of about 1 cm. in diameter (Fig. 5) in which heavy calcium deposits appeared over a seven year period but which drained after a trauma to the chest during an automobile collision, resulting in a cavity of identical size. The sputum, consisting of small amounts of sand-like substance, was positive during the period of drainage. Subsequently the cavity disappeared from view. The great importance of the possibility of drainage—or, clinically speaking, of reactivation—suggests that from roentgen observation the size of the lesion rather than its density caused by calcium content can serve as a fair criterion for possible later developments.

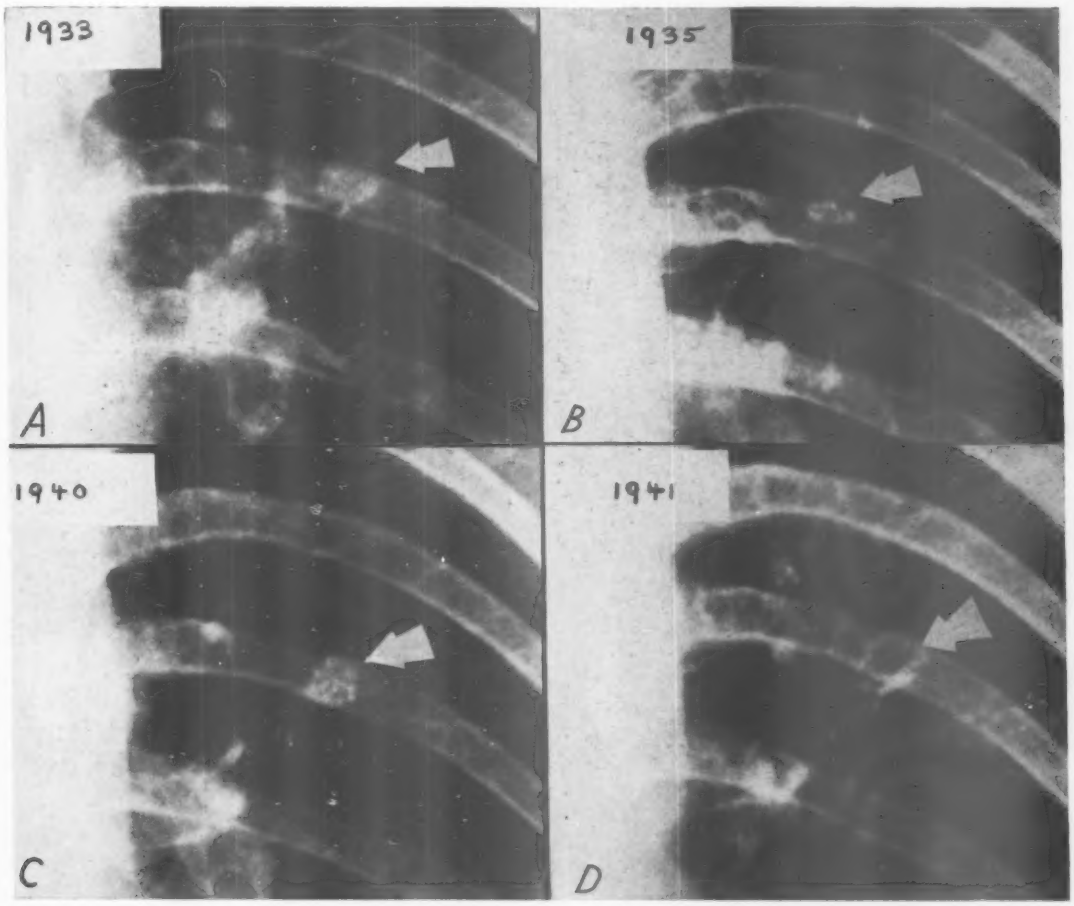

Fig. 5. *A*, well-circumscribed caseous focus of little density, diameter 14 mm. *B*, after two years reduction in size and beginning calcium deposition. *C*, after seven years calcium content increased. *D*, after eight years drainage of lesion following trauma leaving cavity of the same size as that of the original lesion. Cavity has since closed spontaneously without residuals. Patient clinically well.

Since obviously the degree of roentgen-ray density depends upon the amount of calcium salts which have been deposited, it seems desirable to know just how much calcium is needed to produce the roentgen opacity which we are used to associate with calcification. In a small number of speci-

mens with concentric ring configuration the correlation of the intra vitam and postmortem roentgenogram and the macroscopic and microscopic appearance of the specimen as well as the results of chemical analysis were possible. A dense rim which was visible on roentgenograms of an excised specimen (Fig. 6) could not be seen on the clinical roentgenogram, indicating that there is a limit to the degree of calcium demonstrable through the tissues of the thoracic wall. Although the central part of some of these lesions was of much greater roentgenographic density than the peripheral part, it proved to be caseous on postmortem examination and could be removed easily with a needle, whereas the periphery was hard and calcareous. This phenomenon was observed in many similar specimens (Fig. 7). Chemical analysis corroborated the impression gained from roentgenographic examination; in one specimen, for instance, the following chemical values were obtained: the soft central part contained much more calcium per 100 grams of dry tissue than the hard periphery (Fig. 8). Why one lesion or part of the lesion with high calcium values can remain soft and caseous, while another focus or another part of the same focus, comparatively low in calcium, becomes petrified or ossified, is as yet unexplained.

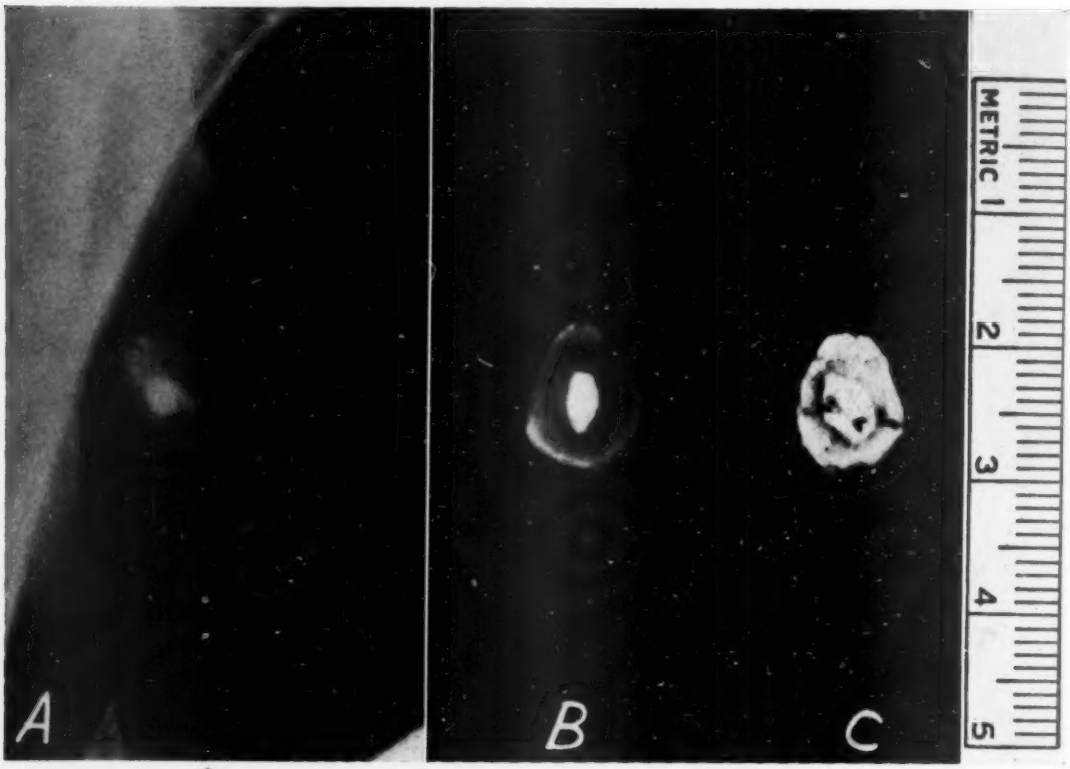

FIG. 6. Intra vitam roentgenogram of tuberculous lesion, diameter 16 mm. Central density signifying abundant calcium deposits. Peripheral calcification is faintly suggested by traces of increased density. *B*, roentgenogram of the excised specimen. The peripheral calcium deposits are clearly visible. The difference between *A* and *B* indicates the failure of the average clinical chest roentgenogram to show moderately dense calcium accumulation. *C*, cut surface of the specimen. The central part containing the much greater amount of calcium was soft and could be removed easily. The periphery, although much poorer in calcium, was thoroughly calcareous.

The curve shown with the specimen in Figure 8 is the density record obtained with

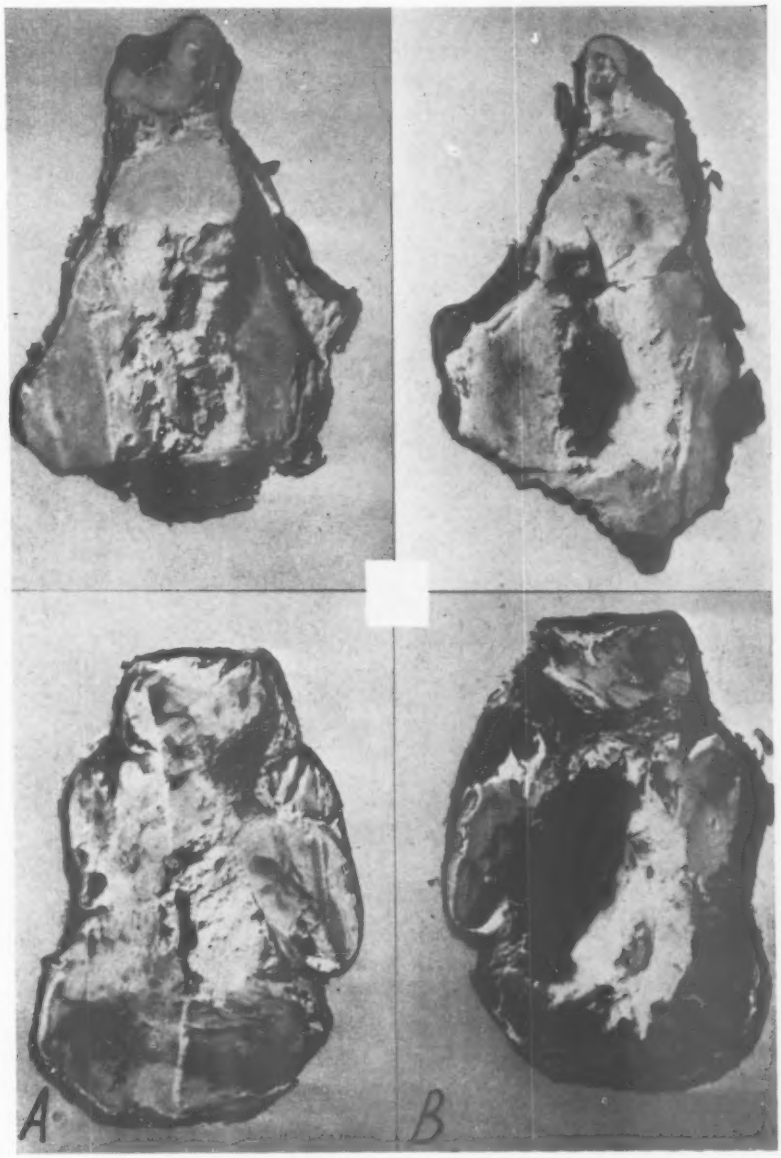

Fig. 7. Cut surfaces of two halved lesions similar to the one shown in Figure 6. *A*, Halves of the specimens with the chalky, partly caseous center walled by thick petrification. *B*, The other halves of both specimens after easy removal of the central part.

a specially constructed densitometer[1] permitting measurement through an opening of 1 mm. in diameter. It registers the relative densities within the lesion with an accuracy which cannot be obtained by the eye. In a large number of such experiments it was shown that lesions of low density can contain considerable amounts of calcium—enough, in fact, to be compatible with petrification although the roentgen density may be lower than that produced by non-calcious pulmonary lesions. The question then arises, if calcification in the strict sense of the word is an accumulation of calcium salts, can it be reliably diagnosed as such roentgenologically? The answer is in the negative.

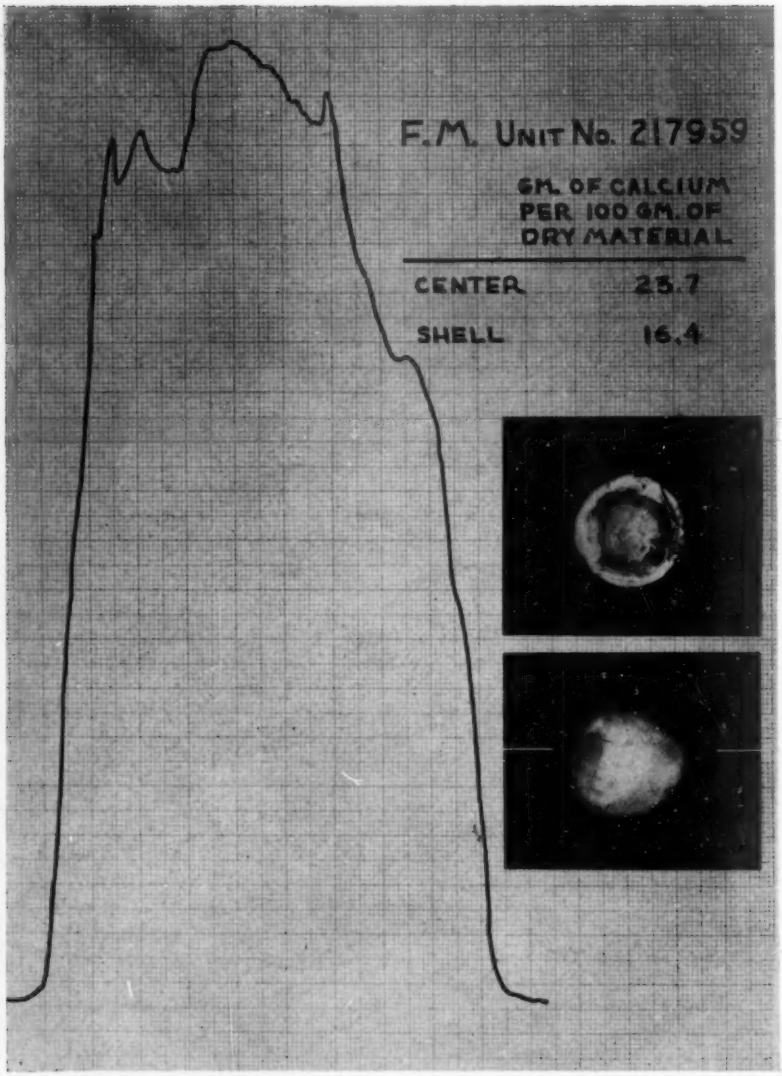

FIG. 8. Comparison of roentgenogram of a calcified specimen of 15 mm. diameter with appearance of the cut surface of the tubercle. Calcium content considerably higher in the soft chalky center than in the calcareous outer shell. Densitometer curve obtained along a line indicated on both sides of the roentgenogram.

EXPERIMENTAL OBSERVATIONS

The lowest calcium content demonstrable with any roentgen-ray technique was calculated* as 0.074 grams of calcium phosphate or 0.017 gm. pure calcium in aqueous solution per cm.^{2} of projection area. It can be shown experimentally that calcium values per space may be much in excess of the calculated figure and yet fail to cast opacities conforming to the clinical-roentgenologic concept of calcification.

Three cellophane-floored cylinders (Fig. 9) of 1 cm., 3 cm., and 6 cm., respectively, in height and of a respective volume of 5.3, 15.9, and 31.8 cc. were filled with calcium phosphate containing 0.23 gm. of pure calcium per cc. Densely packed with calcium phosphate they contained 0.21 (*A*), 0.63 (*B*) and 1.26 (*C*) gm. of calcium per cm.^{2} of floor area. The cylinders were exposed to roentgen rays together with specimens of

* Personal communication of Dr. Wilhelmj (deceased), Department of Physics, University of Chicago.

tuberculous calcification. The first specimen, a large conglomerate lesion, had a projection area of 9.7 cm.^{2} and a maximum thickness of 15 mm. In part, the opacity cast by the specimen seems equal to that of the highest cylinder, although its volume was just a little more than one-third of the cylinder volume and its greatest thickness just one-fourth of the depth of the cylinder. Its chemical content was 0.215 gm. pure calcium per cc. or 0.30 gm. of calcium per cm.^{2} of area.

The second specimen (Fig. 10) had 3 cc. or a little more than half of the volume of the smallest cylinder; its greatest depth was 13 mm. or somewhat more than the depth

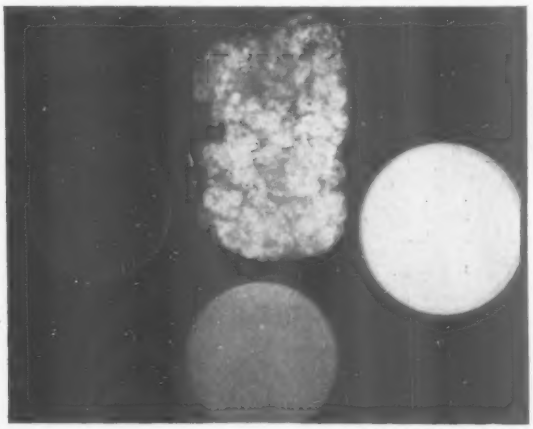

Fig. 9

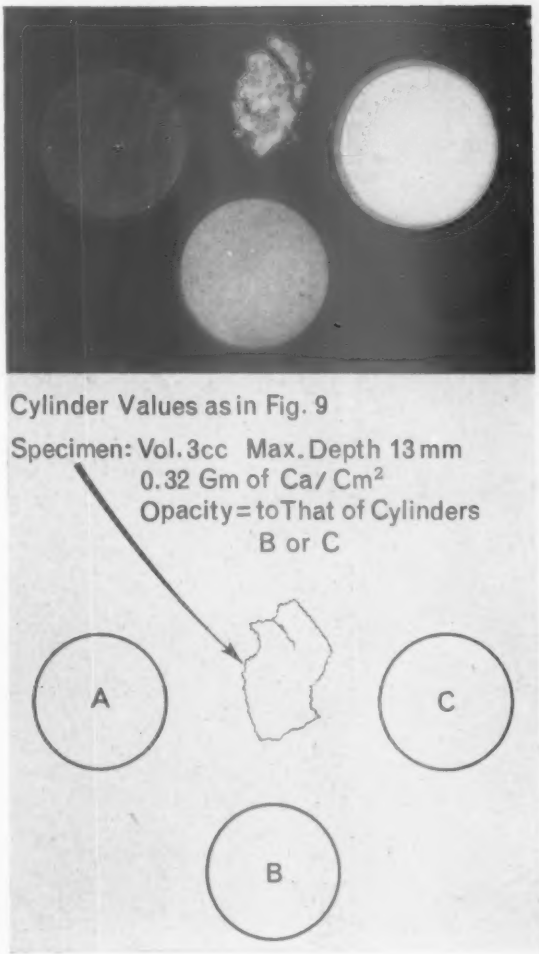

Fig. 10

of the same cylinder. But it also equalized in opacity either the 3 cc. or 6 cc. cylinders of a multiple volume. The chemical content of this specimen was 0.32 gm. calcium per cm.^{2} of projection area. In both of these specimens the pure calcium content per area was only little in excess of that in the control cylinders but exposed to roentgen rays through only a fraction of the depth of calcium accumulation in the cylinders which corresponded in density.

The third specimen (Fig. 11) had an area of 0.18 cm.^{2} and its depth was 4 mm., or less than one-half of the smallest cylinder. Its calcium content was 0.134 gm. per cm.^{2} or little more than one-half of that of that cylinder. Although the specimen was calcareous, its density did not conform to the

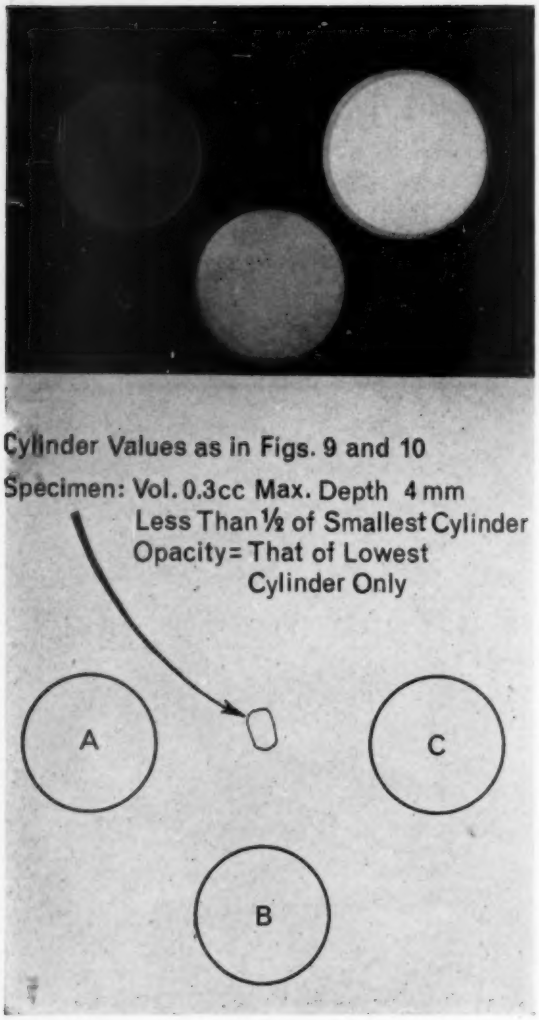

FIG. 11

roentgenologic standard of calcification.

The conclusion from these experiments was that in order to register with an opacity compatible with our arbitrary roentgen standards for calcification, a tuberculous lesion has to be packed with calcium salts. On the other hand, low density values do not signify the absence of calcium; in fact, calcium may then be present in amounts sufficient for complete petrification although roentgen examination could not recognize them as calcifications. In clinical roentgen-ray interpretation this inevitably leads to the diagnosis of significant lesions, when in reality there is a thoroughly petrified focus. Roentgenological mass surveys, constantly growing in scope, vividly demonstrate the need for better understanding and appraisal of small roentgen-ray opacities. They are the inevitable source of prognostic difficulties which in part can be eliminated only by subsequent roentgen observation.

In a series of animal experiments, several aspects of tuberculous calcifications were investigated. The details of these attempts are not within the scope of this paper; however, all of the experiments served to demonstrate the early occurrence of calcium deposition in tuberculous tissues and allowed for a comparison of their chemical calcium content with the degree of tuberculous involvment in various organs.

In a total number of 108 animals, 65 rabbits and 43 guinea pigs, the calcium content of the organs most regularly involved by tuberculosis—lungs, liver and spleen—was compared with the amount of tuberculosis observed on macroscopic examination and appraised by an arbitrary scale of 1 plus to 5 plus. Twenty-two animals in each group served as controls. A summary of the results (Table 1) shows the calcium values in the tissues of rabbits as strikingly corresponding to the amount of tuberculosis found on gross examination. Abundant calcification as early as three to four weeks after infection makes the rabbit the more suitable test animal, but in guinea pigs, too, the figures show the correlation between early disease and calcium, although calcium is deposited more slowly and only in scant amounts in the organs of that species. Other investigators[11] have acknowledged the early occurrence of calcium changes in the tissues of tuberculous animals. Coldwell[4] found as much as 15 per cent calcium in caseous material "in which there were no macroscopic evidences of calcification other than the presence of sand-like particles." However, these authors did not stress or accept its significance for the healing process. The findings presented here should dispose of the contention that calcification is a late or after effect to the healing of tuberculosis.

Artifical stimulation of calcification in

tuberculous tissues would be a great boon to the healing of the disease. Medication with calcium-containing preparations and dietary therapy with foods rich in calcuim or with vitamins could not be proved to have striking results, if any. The mechanism of calcium deposition is not explained, but it is clear that attempts to enrich the blood with the mineral have been of little avail. The calcium level in the blood remains constant. It seems an acceptable theory that[6] "the failure of the body to deposit lime around the tuberculous areas is to be ascribed not to a deficiency in blood calcium, but rather to an inability of the cells of the tuberculous area properly to utilize available calcium."

To be able to induce such utilization would lead far toward new progress in phthisiotherapy.

Table I

CALCIUM VALUES (GRAMS PER 100 GRAMS DRY TISSUE) COMPARED TO MACROSCOPIC EVIDENCE OF TUBERCULOSIS

	Lung		Liver		Spleen	
	Number Animals	Calcium	Number Animals	Calcium	Number Animals	Calcium
Normal Rabbits	22	.059	16	.019	16	.026
T B+	10	.054	10	.070	7	.043
T B++	2	.086	5	.044	7	.048
T B+++	4	.125			1	.050
T B++++	10	.182				
T B+++++	17	.521				
Normal Guinea Pigs	22	.039	17	.014	8	.026
T B+	8	.043	6	.036	5	.029
T B++	2	.030	10	.024	6	.037
T B+++	7	.044	6	.031	9	.033
T B++++	3	.052	5	.106	8	.068
T B+++++	1	.074			4	.191

3. The term "calcification" as used in roentgen diagnosis is arbitrary. Absence of a certain degree of density with any roentgen-ray technique does not rule out the presence of fairly abundant calcification. Experimental evidence is presented to show that in order to produce the degree of density customarily attributed to calcification, a lesion has to be packed with calcium. Lesions not commonly identified roentgenologically with calcification may contain considerable amounts of calcium.

4. The occurrence of calcareousness (petrification) does not depend entirely upon the amount of calcium present in the lesion. Lesions or part of such lesions containing large amounts of calcium per space may be still soft and caseous and therefore are capable of unfavorable development. On the other hand, foci of relatively low calcium content may be calcareous and therefore innocuous.

SUMMARY

1. Calcification of caseous tuberculosis is one of the essential healing processes of the disease.

2. Calcification is not an incidental after effect to an already accomplished healing by fibrosis, but begins early in the development of caseating tuberculous lesions. Experimental evidence in support of this contention is found in the increase of calcium in early tuberculosis of animal tissues.

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MUCOSAL STUDIES IN COLITIS DUE TO PARASITES*

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THE problem of colitis due to parasitic infection, particularly the ameba, involving a high percentage of our population and many of our returning veterans, presents an immediate challenge to roentgenology. The word of Manson-Bahr (1940), "It is disappointing to record that only unsatisfactory assistance can be obtained by this method," and similar statements found in the literature, should not be regarded as final but rather as an exhortation to reopen the entire problem of parasitic, mycotic, and bacterial infection in its roentgenological aspects. Cooperation between the microbiologist and the roentgenologist is a source of inspiration and instruction to both and will place the diagnosis of colitis, which Axel Munthe once described as frequently the stopgap of an uncertain abdominal diagnosis, on a firmer basis as to cause, involvement, and efficiency of treatment.

Reviewing such roentgenological observations as have been made, we find as the most prominent roentgenological sign of amebiasis hitherto recognized, the cone-shaped, deformed cecum pole described by Bell (1936), who considered it as highly suggestive of amebiasis. In a recent publication Golden and Ducharme confirmed the findings of Bell and of Weber on 30 patients. In 21 of these cases *Endamoeba histolytica* was found. Other observations are those of Vallarino describing filling defects in amebic infections in all clinical stages of the disease, whether mild or severe. Smithies, who studied many cases of amebiasis roentgenologically, stated that 44 per cent of them showed intestinal lesions of the ulcerative type. More cautious and circumspect appears Ikeda's study in which he found the changes varying with the degree of infection, whether ulcerative, fibrous, or granulomatous. In the early stages no changes were noted, later saw-tooth-like projections along the wall of the colon, and still later fine, feathery filling defects were seen. He also observed the characteristic cecal deformity, and shortening and contraction of the ascending colon with induration of the walls and filling defects. The roentgen picture, according to Ikeda, while not strictly diagnostic, determines the location, the degree, and the extent of the involvement.

Weber (1938) described the abnormal patency of the ileocecal valve, and the particular rush of barium into the ileal loop, the suppression of haustration, shortening and narrowing. Case described a progressively diminished movement of the right diaphragmatic excursion found in amebic infection of the intestines.

The more severe forms of amebiasis, as found in Africa and Asia, are described by Spéder from French Morocco on oral examination as: (*a*) normal in appearance; (*b*) atonic; (*c*) accordion-like; (*d*) en chénille, (*e*) dechiqueté, (*f*) rigid, (*g*) filiform.

From the Middle East, Druckmann and Schorr describe forms of constriction and narrowing of segments of the colon in the localized type of amebiasis with a "more or less normal mucosal pattern."

Other authors have deliberately abstained from any attempt to differentiate the various types of colitis beyond the general term "ulcerative colitis," including in it all types of bacterial infection, parasites and dietary deficiency. While fully aware of the complexity of the problem, we feel that further attention to detail and a meticulous technique, the combination of a thorough microbial and parasitologic study as well as the demonstration of visible changes in the colon, will help to place the diagnosis of colitis roentgenologically on a

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firmer basis and to analyze certain forms of it. We are already able to say that many cases previously diagnosed as irritable colon, nervous colon, or colitis of unknown origin, are due to parasitic, mycotic, or bacterial infection.

We have learned to attach significance even to minor changes of the mucosal pattern and have found further confirmation that the roentgenological picture of ulcerative colitis is not rarely observed in combination with amebiasis, just as it is frequently found in bacillary dysentery, according to Felsen.

There is no way to determine the etiological factor of an infectious intestinal lesion solely by clinical examination. It is true that the clinical textbook picture of amebiasis (Type 4 according to Craig) will be more easily diagnosed as such. The same can be said of the typical Shiga-Kruse bacillary dysentery. Chronic forms, however, mainly those which are accompanied by a variety of signs ranging from intermittent outbursts of diarrhea or protracted constipation to general nervousness and fatigue may be evoked by a considerable series of organisms (Table 1).

TABLE I

I. Bacterial	II. Parasitic	III. Mycotic	IV. Others	
Shigella	Amoeba	Monilia	Vibrio	Treponema
Salmonella	Flagellata	Zygomyces	Staphylococcus	Helminths
Paracolon	Coccidium	Actinomyces	Streptococcus	Schistosoma
Proteus	Balantidium	Aspergillus	Mycobacterium	Trematoda
	Plasmodium		Alkaligenes	Strongyloides
	Leishmania			

These etiological factors cause the broad complex of symptoms which is designated as dysentery and which often gives rise to sequelae such as mucous colitis and ulcerative colitis. Once such sequelae develop, even the laboratory diagnosis becomes more difficult, and in many cases impossible. Cocci and coliform organisms, or *Proteus* and *Pseudomonas*, small intestinal flagellates and yeast-like fungi dominate the picture. Due probably to the action of bacteriophages and phagocytic body cells, the causative agents are difficult to cultivate, or in the case of protozoans, difficult to find in the feces.

Our material consists of 98 cases of protozoan and 15 cases of bacillary (*Salmonella-Shigella*) infections, diagnosed during the last ten months in the laboratories of the Mount Sinai Hospital. Out of the 98 patients infected with protozoa, 32 had a roentgen examination and 24 have certain roentgenological findings.

In contrast to most previous publications, our own observations are mainly based on surface studies of the mucosal lining; several cases showed also the previously described deformity of the cecum pole and other variations of outlines after filling. Relief studies are, in our opinion, the only method by means of which finer surface changes can be seen and filling defects can be studied in their relation to folds. We have not neglected entirely other methods such as air inflation but we found them of little value in the diagnostic problem of parasitic colitis.

Our first difficulty here was the establishment of the norm. This is the more necessary as Knothe's monograph on the mucosal pattern leaves many questions open and with the introduction of pharmacological tests as well as heat and cold influences, vagus irritation and other types of activation and irritation, does not give a clear conception of what should be called normal.

The two types of folding, transverse and longitudinal, are first of all the expression

of the two muscular forces: the circular musculature and the longitudinal musculature. As the longitudinal musculature is characteristically arranged in three bands spaced 1 inch apart, their contraction results in forming an inner axis which holds the longitudinal folds which we propose to name axis folds. The haustrum is the direct consequence of the enclosure of the long colon within these three shorter bands giving the effect of a puffed sleeve.

There has been considerable controversy as to whether the haustrum is a functional or anatomical unit. Some observers were so much impressed by the perpetual restlessness, the haustral flux, and the haustral effacement, that they called the haustrum a functional unit and the plicae semilunaris functional structures. The presence of haustra in the newborn, in paralytic ileus and in obstruction is, in our opinion, sufficient proof that they are anatomical structures. Polymorphous haustration and haustral flux are normal phenomena. Absence of haustration, particularly in the ascending and transverse colon, is generally recognized as a sign of pathology. Within the haustral pressure chamber, the mucosal folds are mainly transverse or composite. They are harmonious, showing gentle curves and arborizations. The axis folds can be followed even through the haustral folds, and they dominate the interhaustral intervals. In the rectum, sigmoid and lower descending colon we find prevalent the type of pattern called simple folding by Sarasin. From such a pattern we find abnormal deviations as to size, number and direction of folds. Taking into account a considerable number of pattern variations due to autoplastic movement (Forssell), the basic structure is as preserved and recognizable as the human face is in spite of its emotional variations.

To be called pathological a pattern has to show either considerable persistent widening of folds, or disorientation of the pattern, or absence of folds with areas of ulceration or granulation. These three types of pathological pattern are found in various

Fig. 1. Case 1. Widening and disorientation of folds in cecum and ascending colon in a case of amebic colitis.

types and stages of inflammation. In the mildest form of deviation we see frequently a tight packing of folds around the longitudinal axis giving the bowel a barbed wire appearance, their position being more angular, the haustral separation frequently indistinguishable. While this picture impresses the observer as an abnormal one, its interpretation remains uncertain. It is variously interpreted as irritable colon, as a reactive stage of the normal colon to various local and general causes such as allergic, nervous, toxic and also as true colitis. Only in one case of amebiasis have we found such a pattern of tightly packed transverse folds resembling the microscopical arrangement of chromosomes and have discarded it as unreliable. The borderland between the normal and early pathology is always an uncertain ground, and Sarasin's postulate that these changes must be sharply differentiated from changes due to colitis is still far from realization.

We reach firmer ground in the stage of

FIG. 2. Case II. Coarseness of the mucosal pattern, deformed cecum pole, spasticity and irregular haustrations in a veteran with signs of amebic dysentery.

swelling and widening of the mucosal folds, so well illustrated in Case I.

CASE I. This case of proved amebic colitis shows the widening as well as the disorientation of folds, particularly in the ascending colon and cecum. Like a flight of winding stairs, the mucosal folds ascend with sharp angles. There are many irregularities, the axis folds have disappeared and a soft double line indicates the outlines of a swollen or indurated wall in the area of the ascending colon and cecum pole. Proctoscopy revealed an edematous, easily bleeding mucosa but no ulcerations. *Endamoeba histolytica* was found in the stools. The history is that of abdominal pain persisting for years, and constipation.

CASE II. A war veteran came to us because of attacks of diarrhea and blood found in his stools. Here again the mucosal pattern showed, particularly on spot roentgenograms, disorientation and coarseness of the mucosal pattern, irregular haustration and the "deformed cecum pole." The changes were localized mainly in the lower ascending colon. The proctoscopic examination showed patches of edema, no visible ulceration. The stool examination revealed *Endamoeba histolytica.*

CASE III. This case demonstrates an occurrence which we frequently observe in amebiasis in combination with unusual swellings, localized spasm over the cecum pole and ascending colon revealing an irregular, feathery, mucosal pattern. The patient, a nurse, had bloody diarrhea for a long time and ill defined abdominal complaints. The incomplete filling, spasticity and tenderness persisted on repeated examination; the bowel wall was thickened in the area of the cecum and ascending colon.

Stool examination: *Endamoeba histolytica* repeatedly found.

CASE IV. This case demonstrates the same type of spastic contraction extending to Cannon's point, as a sign of increased irritability in the proximal neurological unit of the colon. The mucosal pattern in the cecum pole is disoriented and loosely woven, the wall appears as double line, "wall effect." The patient, a housewife,

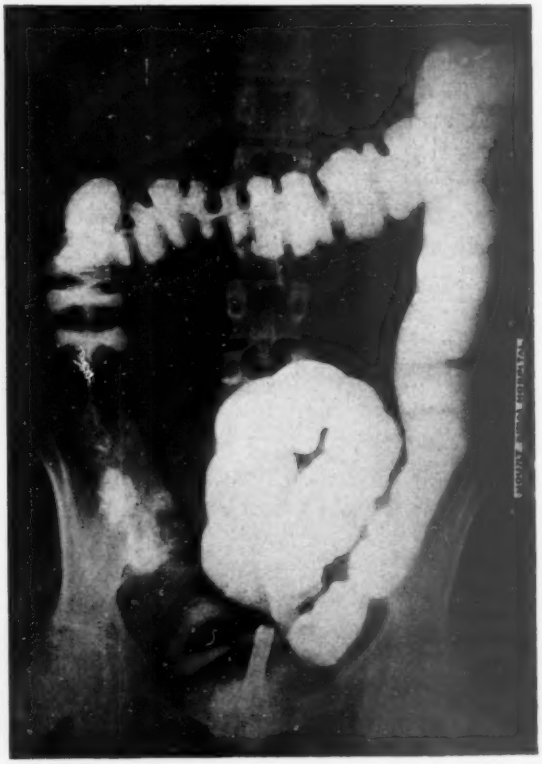

FIG. 3. Case III. Localized spasm over cecum and ascending colon revealing an irregular loose mucosal pattern in a nurse showing amebic dysentery.

aged thirty-eight, had amebic dysentery in 1937 and was temporarily cured. She complains now of pain in the upper back radiating to the left shoulder; she has been constipated and has complained of intermittent nausea for a long time.

Stool examination on two occasions showed *Endamoeba histolytica;* later on, only degenerative forms.

Case v. The swelling of the entire transverse colon with mucosal changes mainly visible in the sigmoid area is presented in this case. Vis-

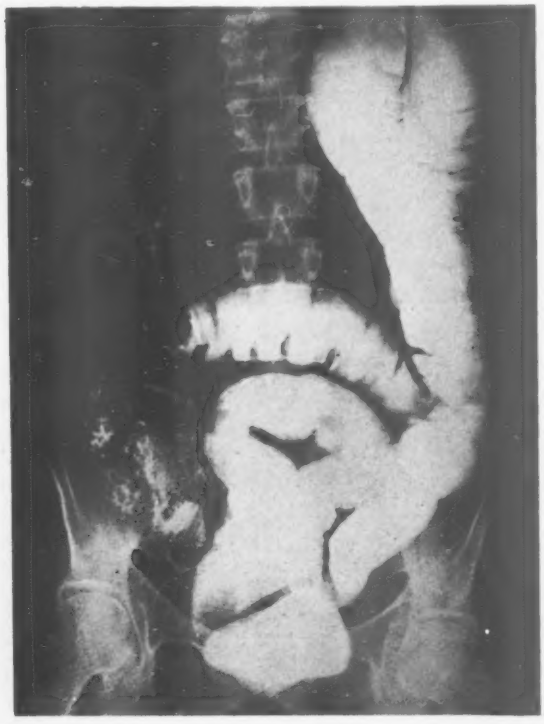

Fig. 4. Case iv. A similar picture of spasticity, incomplete filling and disoriented mucosal pattern over the ascending colon and cecum up to Cannon's point in a patient who has a recurrence of amebic infection. *Endamoeba histolytica* found.

ualization of the cecum pole not possible. Rigidity and mucosal swelling in sigmoid and descending colon marked. The patient, a nurse, aged twenty-two, developed nausea, lower abdominal pain, loose bowel with blood and mucus in the stools.

Proctoscopy showed edematous hyperemic granular surface. *Endamoeba histolytia* was found in the stools.

Case vi. Another demonstration of a local-

Fig. 5. Case v. Mucosal swelling over the entire transverse and descending colon; mucosal changes and rigidity, particularly over the sigmoid. Clinical signs of colitis. *Endamoeba histolytica* found.

Fig. 6. Case vi. Similar changes of mucosal pattern with persistent narrowing of the sigmoid in a case of amebic dysentery.

ized change of the mucosal pattern combined with persistent narrowing of the sigmoid, but

Fig. 7. Case vii. Loose mucosal pattern, no cecal deformity in a veteran with symptoms of colitis. *Endamoeba histolytica* positive.

without visible cecal changes, is seen in this case of amebic colitis. The patient, aged forty, had intermittent watery diarrhea for eight months, five to six stools a day; cramping pain in the abdomen.

Proctoscopy not done. *Endamoeba histolytica* found in the stool.

Case vii. The paucity of the mucosal pattern in the cecum and ascending colon is the one pathological sign in this case and is caused by a wider system of fewer folds. The patient, a veteran of the Pacific Theatre in World War II, has a history of dengue fever. He developed abdominal cramps, epigastric tenderness, then began having frequent bowel movements with frank bleeding.

Proctoscopy showed slight swelling and hyperemia of the rectosigmoid mucosa. In smears taken during proctoscopy *Endamoeba histolytica* was found.

Case viii (Fig. 8, *A* and *B*). A very similar, if not identical, picture of widened, irregular mucosal folds over the entire ascending colon accompanied by a deformed cecum pole and a "wall effect" (soft double contours) along the ascending colon and descending colon was found in this case of yeast infection. The patient is a returned veteran of World War II complaining of cramp-like pain in the abdomen with explosive diarrhea, two to three watery stools a day. The roentgen examination suggested amebic colitis, yet no amebae were found, but instead a *Monilia* infection.

Case ix. The combination of ulcerative colitis and amebiasis is illustrated in this case. The patient had a history of mucous bloody diarrhea for fifteen years. Proctoscopy revealed blood oozing from an eroded surface. *Endamoeba histolytica* was found. The picture is not that of an ulcerative colitis of such long duration. It suggests that this was first an amebic infection which untreated developed into an ulcerative colitis.

In such an unhealthy combination of amebic

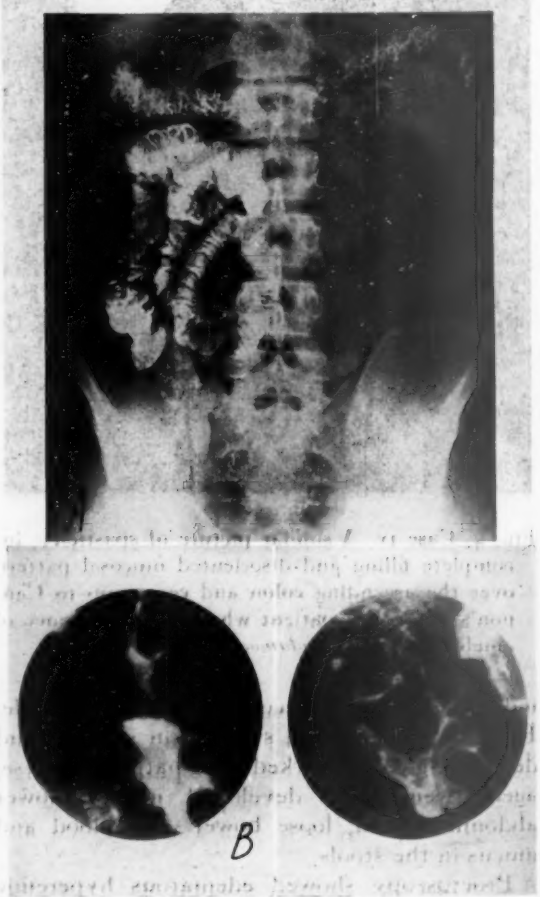

Fig. 8, *A* and *B*. Case viii. Paucity of mucosal pattern in ascending colon, wide folds in cecum pole in a case of yeast infection (*Monilia*).

infection and ulcerative nonspecific colitis the ulcerative colitis usually dominates the picture. While the ulcerative process ascends from the rectum, the cecum pole and ascending colon show changes of a different type or degree. The colon thus resembles a candle burned on both ends.

Case x. Such a picture is also seen in Figure 10, originally diagnosed as segmental ulcerative colitis. Mucosal denudation in the descending colon, a moderate degree of mucosal swelling found in the transverse colon, wall infiltration and thickening in the cecal area. Combination of ulcerative colitis and amebiasis has to be considered in such a case. The patient, a female, aged twenty-four, had a history of long-standing diarrhea, bright red blood in her stools. Proctoscopy revealed a normal mucosa. The parasitological examination (done elsewere) was unsatisfactory.

Once we became familiar with such a pattern and its analysis, we recognized it frequently even in its milder modifications and were frequently able to suggest the diagnosis of parasitic infection to a physician who did not suspect such a condition, before the stools were examined. The swelling of the mucosal folds in its range from paucity of the barium lines to spider-like wide distention corresponds to the progressive stages of an inflammatory reaction. In a high percentage of cases the same picture of edematous swelling and easy bleeding was found also at proctoscopy, rectum and sigmoid being frequently involved simultaneously with the cecum. The ratio of involvement of cecum and sigmoid in our observation was found the same as given by James, i.e., 2:1.

Fig. 9. Case ix. Combination of ulcerative nonspecific colitis and amebiasis. *Endamoeba histolytica* found in stools.

Fig. 10. Case x. Segmental colitis, mainly ulcerative nonspecific colitis, but frequently found in amebiasis and ulcerative colitis.

An important conclusion not hitherto known, but demonstrated in some of our roentgenograms, is that the area between cecum pole and sigmoid is not entirely normal in amebic infections, but frequently shows a minor degree of swelling of the folds.

A mild degree of mucosal irregularity was found also in one case of infection with *Diendamoeba fragilis*, and in one case of *Io-*

damoeba infection. This would be important if substantiated by a larger number of cases, as the pathogenity of these infections in man is not generally accepted. The *Monilia* and yeast infections are also scarcely known to the roentgenologist, yet are frequently found in institutionalized patients. One case observed by us, a man recently returned from duty in the Pacific, complained of cramps and explosive watery diarrhea. The colon was normal in outline and filling but showed such mucosal changes and spasticity of the cecal region as to suggest amebic involvement. The stool examination revealed no amebiasis, but yeast infection (*Monilia*) (Case VIII, Fig. 8).

The ultimate aim of our mucosal studies was the direct visualization of the ulcers. We met here with considerable difficulty. Ulcers are present in all stages beyond that of a carrier; the characteristic lesion even in early stages of amebic dysentery is ulceration.

We believe the difficulties in the demonstration are due to the fact that they have, like molehills, a pin-sized opening which leads into the submucous coats, even to the muscularis, and is filled, as specimens in the Army Medical Museum so well demonstrate, with cytolysed material, which may well prevent the contrast medium from entering. The burrowing process underneath the mucous membrane is, according to Craig, characteristic of amebiasis and the ulcers are generally described as "buttonhole ulcers," "sea anemone ulcers," "seaweed sloughs." In distinction to bacillary enteritis and ulcerative colitis, the mucous membrane between the ulcers is preserved in amebic colitis. The wall between the ulcers in amebic dysentery is, according to Manson-Bahr, thinned out and ballooning, and an ulcer filled with contrast medium might have the appearance of a diverticulum rather than of an ulceration. It is at a later stage that the walls become thickened and fibrous.

All these are sufficient reasons to explain why we have to search for the less conspicuous amebic changes hidden in the depth of the cecal sacculations. The demonstration of the mucosal changes is much easier within the simple folding of the better emptying descending colon and sigmoid. Such ulcerations as we were able to visualize without effort were usually those of nonspecific ulcerative colitis. The process begins in ulcerative colitis in 95 per cent, according to Bargen, in the rectum, and like a prairie fire runs continuously upward destroying the mucosal surface. There is frequently observed a temporary arrest at Cannon's point but if not checked the process ascends frequently into the cecum pole and into the last ileal loop. The edema is more marked, the mucous membrane shows very early complete disorientation of the folds, soon to be followed by superficial ulceration.

The character of the ulcers, as seen in Figure 11, is quite different from amebic ulcerations. They are more irregular in form with scalloped, undermined edges; they are larger and more confluent. We have repeatedly observed that the barium does not, as we would expect, fill the crater of the ulceration but accumulates in the crevices and pockets of the residual heavily deformed mucosa. This, we feel, is also the case in Figure 12.

Another phenomenon, the feathery appearance of the outlines resembling the Kerkring folds of the small intestinal pattern, is, in our opinion, due to the contrast medium reaching the denuded muscularis and forming not a mucosal but a muscularis pattern. In the cases we observed, the ulcerations in the developed stage of ulcerative colitis were in the long axis of the colon while in bacillary dysentery and tuberculous colitis they were more transverse in direction. The characteristic appearance of the fully developed *bacillary dysentery* is illustrated in Figure 13, which shows the general transverse direction of the ulcerations, the ill-defined communicating character of the surface lesions and the complete absence of hypertrophy of the intestinal walls. The hypertrophy of the intestinal walls is commonly found in amebic dysen-

tery where the mucosa between the ulcers remains unchanged.

Thus the appearance of the surface changes, the character, location and the direction of the ulcers, is an important point in differentiation. We have presented a few examples here not only to summarize the various changes of mucosal pathology down to the most severe stages of denudation but also because it is quite common to find the picture of an ulcerative colitis superimposed upon an amebic infection. In such case the antiamebic treatment will not effect a cure. It is difficult even to find the ameba at that stage due to the mixed infection and pus cells. The question is raised as to whether the untreated and neglected amebic infection could not go on to ulcerative colitis. Lockhart-Mummery has reported many cases in soldiers of World War I who suffered (in Egypt and Gallipoli) from dysentery, bacillary as well as amebic

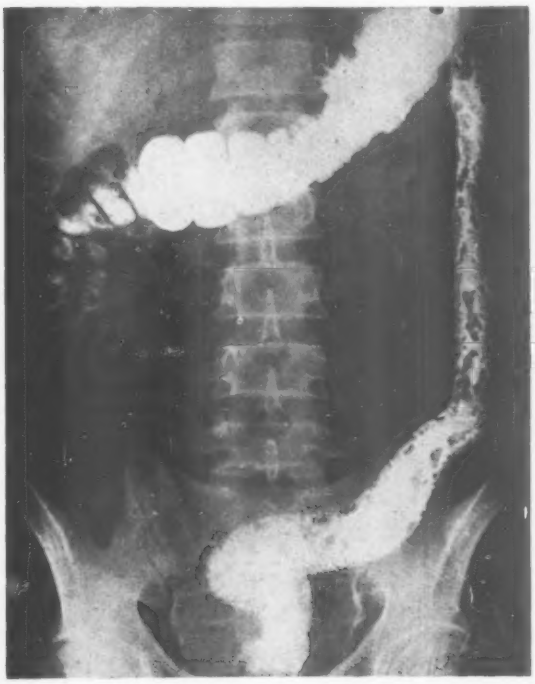

Fig. 11–13. Illustrating various types of ulcerations.

Fig. 11. Longitudinal type of ulcers in ulcerative colitis, ulcers free of barium.

Fig. 12. Barium floating on muscularis, simulating heavy transverse folding in nonspecific ulcerative colitis. Ulcers more longitudinal.

Fig. 13. Ulcerations in bacillary dysentery. Transverse ulcerations, irregular, confluent, no hypertrophy of the bowel walls.

infection, and later on developed typical ulcerative colitis. No amebae were then found, while the symptoms persisted. The finding or absence of parasites alone, therefore, does not entirely classify the colitis case.

The problem of perfect mucosal visualization of the colon is, in our opinion, not yet entirely solved. The colloidal thorium

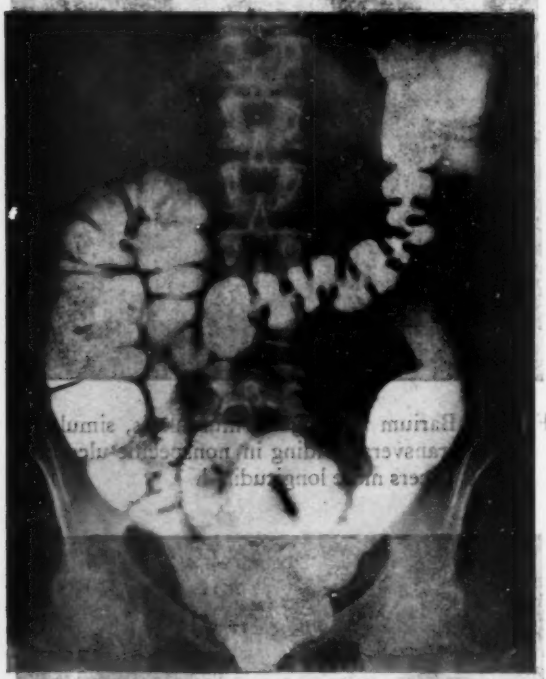

FIG. 14. Corkscrew and spiky haustration frequently observed in amebic colitis resembling the form bandonéon (Spéder). See text.

dioxide is an improvement in its greater adhesive power and more equal distinction after emptying but it is uneconomical. The search for a cheaper colloidal vehicle for the contrast medium should be continued. We have occasionally instead of air inflation, which in our opinion is of little value in the actual diagnosis of colitis, used a method which we might call "observation of the kneaded relief." We have, after incomplete emptying, permitted the bowel to work the barium into the furrows, and obtain thus, if the bowel is not yet indurated, a *working* relief. Such pictures, while not easily analyzed, bring out stronger than the initial pattern, the changes of fold arrangement, disturbed function and contractility.

While mainly concerned here with the study of the mucosal pattern, we take fully into account the filling picture in its various pathological modifications. To the well known description of wall effect, fibrosis, contraction and absence of haustration, we add here two other changes seen repeatedly in amebic infection: one, a corkscrew type of incomplete haustration; the other, a spiky type of flat close haustration, commonly interpreted as prediverticulosis resembling the form bandonéon described by Spéder (Fig. 14).

The roentgenologic visualization of a pathologic pattern will be appreciated by the clinician and the bacteriologist, as the mere finding of parasites does not yet prove a dysenteric condition. Direct visualization of these lesions, their location and extent enable us to judge the degree of involvement and the effect of therapeutic measures. We also have frequently observed a disparity between actual symptoms and degree of involvement, attested by Craig, who found in symptomless carriers occult blood in the feces and necrotic ulcers in the absence of intestinal symptoms. The roentgenologist is usually the first consultant in a case of diarrhea, constipation, cramps or bloody stools. The close attention to detail and the familiarity with the pattern of colitis will enable him to suggest, if not to diagnose, a parasitic infection. Since the establishment of an enteric service at our hospital, we have learned that even minor changes of the mucosal relief have their characteristics and their clinical significance. To make available what we have learned and to open a new interest in the largely neglected studies of mucosal changes in various types of colitis are the aims of this paper.

SUMMARY

In a search for better and more effective aids in the diagnosis and differentiation of colitis, the mucosal pattern of 32 cases of parasitic infections of the colon was studied.

In a high percentage of these cases, mucosal changes, such as spider-like widening and derangement of folds, were found in typical localizations, particularly in the cecum pole, ascending colon and sigmoid. Increased spasticity was observed in these areas, in combination with mucosal changes sometimes taking the form of the previously described cone-shaped cecum pole. Not only severe but also milder types of *Endamoeba histolytica* infections (amebiasis proper) and one case each of *Diendamoeba fragilis* and of *Monilia* invasion showed deviations from the normal.

Changes in the cecal area and lower ascending colon combined (in a ratio 2:1) with deviations from the normal in the sigmoid are strongly suggestive of protozoan infection. Continuous involvement of the colon ascending from the rectum and sigmoid suggests ulcerative colitis. The character of the various ulcerations provides another point of differentiation. The demonstration of amebic ulcerations in the cecum pole in a clear picture is barely possible with the contrast media which are available today.

Many cases previously diagnosed as irritable, nervous or spastic colon have proved to be parasitic infections. It is important to emphasize that the clinical symptoms do not always parallel the degree of the roentgenologically demonstrable actual pathology.

The coexistence of amebic colitis and ulcerative colitis, which is not too rare, is diagnosed from the roentgen appearance showing continuous involvement of the colon when *Endamoeba histolytica* is present in the stools. Antiamebic treatment will not cure such a colitis. The degree of involvement and the efficiency of treatment can be followed by meticulous mucosal studies. Lack of a sufficient number of roentgenological examinations in bacillary dysentery does not at the present time permit the inclusion of this type of infection. They will be reported later on.

The improvement in laboratory methods in the diagnosis of diarrheal incitants must be paralleled by an improvement in the roentgenologic technique. It is believed that the increased demand for correct diagnosis in diseases of the colon can be partially satisfied by a thorough roentgen examination.

The authors are indebted to Dr. Oscar Felsenfeld and Miss Viola Young formerly of the Mount Sinai Hospital Research Foundation for the study of the stools of these patients and for many helpful suggestions.

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AN UNUSUAL CASE OF RICKETS

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THE characteristic woolly type of renal rickets was first described by Teall and Parsons in England about twenty years ago. As noted by these authors, the roentgenological findings were confined chiefly to the skull and metaphyseal regions of the long bones. These regions were depicted as elongated with irregular ossifications, and a peculiar stippled woolly appearance. The affected areas were markedly deformed and although the metaphyses were longer than those seen in rickets, they were neither spread out nor cup shaped. The bone also appeared eaten away in the involved areas. In most of the joints the lesion was asymmetrical. The roentgen changes in the bones were best seen in the knees, wrists, and ankles. Skull roentgenograms sometimes showed extensive thickening of the cranial vault and a widening of the normal diploe. Also there was a minute stippling scattered throughout the vault as sometimes seen in hyperparathyroidism. Since then, the stippled woolly appearance seen at the ends of long bones, with the associated deformities, has been considered pathognomonic of renal rickets.

Recently there came under observation on the Pediatric Service of Dr. L. S. Boyd and Dr. B. R. Irving, City Hospital, Welfare Island, a Negro girl who presented all the roentgenological manifestations described by the English authors, yet had no evidence of renal dysfunction, and who responded well to an antirachitic regimen. The findings are recorded in the following case report.

CASE REPORT

The patient, M. G., a colored female, aged seven, one of four siblings, entered the hospital in March, 1946, with the chief complaint of deformities of the hands, feet, and knees. The patient's mother stated that the child first attempted to walk at fourteen months of age, but found that she could only waddle with a rolling motion. At the same time she first noted deformities of the wrists, ankles, and knees. The deformities gradually became more pronounced, and the affected joints became swollen and painful. The child began to talk between the age of two and a half and three years, but appeared to be tongue tied, and it was further noted that she had a slurring of her speech. The mother claimed that the child's diet was adequate and included cod liver oil and orange juice.

On physical examination the patient was found to be a deformed seven year old colored female, who had a normal temperature, pulse and respiration, and whose blood pressure was 85/65. Her weight was 49 pounds, and her height was 45½ inches. She was unable to walk and could stand only with support. Mentally she appeared somewhat below normal, and she showed evidence of unstable emotional behavior. She reacted very poorly to stimulation and pain.

The patient's skull showed marked prognathism with flattening of the nose, and bossing of the frontal bone. There was a moderate protrusion of the malar prominences and mandible. The chest showed flaring of the lower ribs, and rachitic rosary was observed. At the level of the seventh anterior ribs the chest cage was 20 inches in circumference, while at the level of the lower costal margin it measured 22 inches. The patient's spine was markedly scoliotic to the right in the lower dorsal region. In the remainder of the skeletal system, the changes were most apparent in the shoulders, hips, knees, wrists, and ankles.

She was able to abduct the arms to only about 35 degrees. The wrists had typical silver fork deformities with posterior angulation of the distal radii and ulnas. Motion at the wrists was normal despite these deformities. Internal and external rotation of both thighs was limited. There were noticeable genu valgum deformities of both knees, while the ankles and feet were in marked inversion. The legs were of equal length. Both calf muscles appeared to be moderately atrophied. The remaining systems were essentially negative.

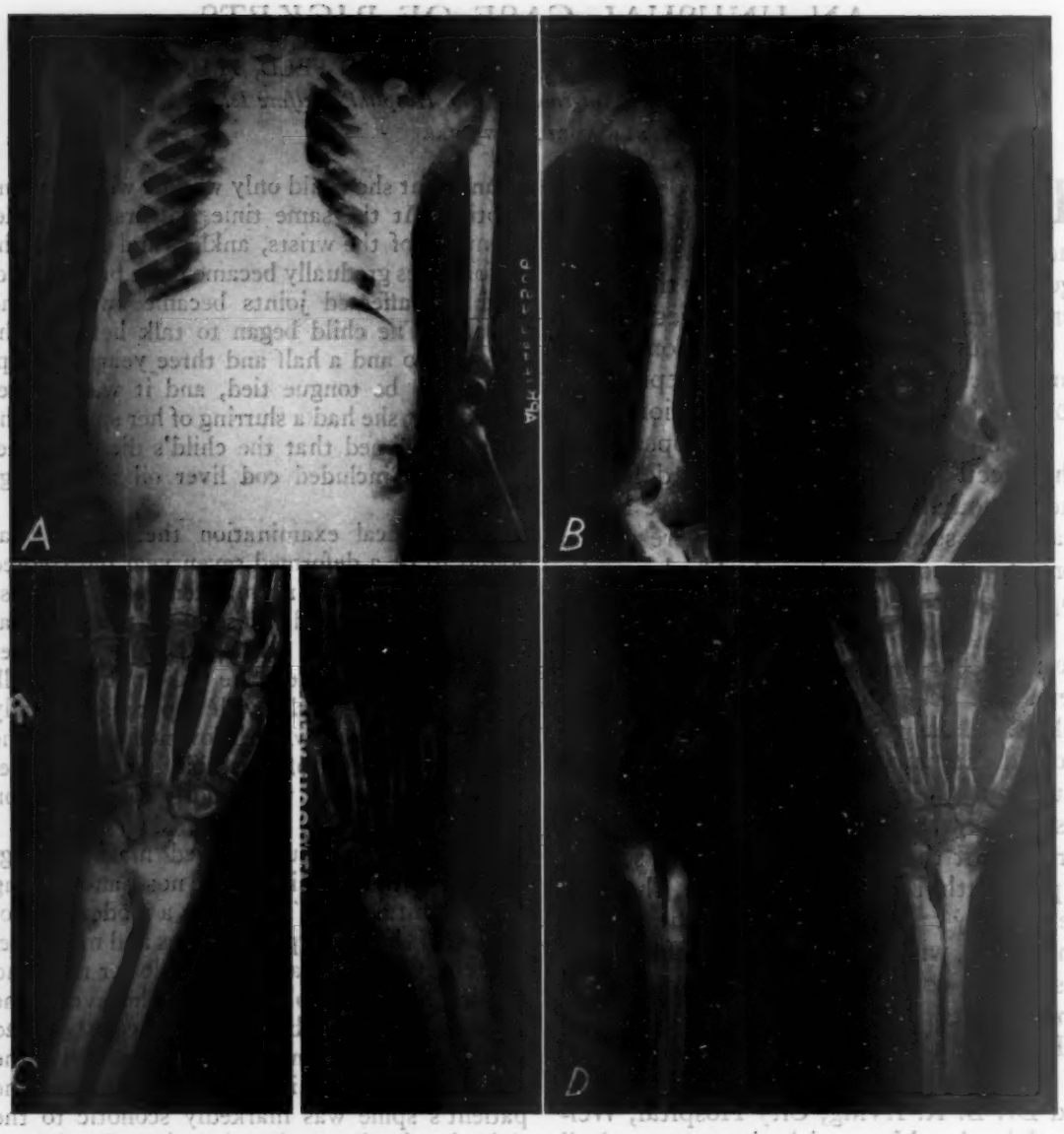

FIG. 1. *A*, chest and proximal humeri April, 1946. There was widening and cupping of the ribs at the costochondral junctions. The proximal humeri were stippled, and showed the typical woolly appearance. *B*, humeri in March, 1947, showed marked increase in calcification at their proximal ends. *C*, wrists in July, 1946. There was a characteristic stippled woolly appearance at the distal metaphysis of the radii and ulnas as well as marked bony deformities. *D*, wrists in March, 1947. Here the diaphyseal ends of the radii and ulnas have acquired more calcium and the deformities are less apparent.

Laboratory findings showed normal urine and blood count on repeated examinations. On admission blood non-protein nitrogen was 29 mg. per 100 cc., blood sugar 88 mg., blood calcium 9.6 mg., and phosphorus 6.9 mg. The serum globulin was 2.2 mg., serum albumin 4.3 mg., while the alkaline phosphatase soon after admission was 91.2 Bodansky units.

The case was considered most probably one of rickets and the patient was placed on an antirachitic regimen.

Preliminary roentgenograms of the skeletal system showed the following: There was generalized thickening of the cranial vault with a widening of the diploe and obliteration of vascular markings. The cranial vault had a stippled appearance similar to that seen in hyperparathyroidism and diffusely arranged throughout.

FIG. 2. *A*, intravenous pyelogram in April, 1946. Five minutes following the injection of the dye, the kidney pelves, calices, and ureters were normally visualized. (Note that the proximal femurs bilaterally show coxa vara deformities, while the heads and necks give the typical stippled woolly appearance.) *B*, in March, 1947, the femoral heads and necks showed marked calcium deposits, although still deformed. *C*, the knees in April, 1947, had moderate genu valgum deformities with some stippling at the distal diaphyseal ends of the femurs and to a lesser extent the proximal tibias. (Note the asymmetry of these joint changes.) *D*, the knees in March, 1947, were much less deformed and the bony structure appeared almost normal.

The cervical, dorsal, and lumbar vertebrae showed a minimal degree of osteoporosis, and there was a moderate degree of scoliosis of the lower dorsal spine to the right. The ribs showed a moderate degree of widening and cupping at the costochondral junctions as seen in rickets.

In the proximal ends of the diaphyses of both humeri was a combination of destructive and productive changes, giving the metaphyseal areas a characteristic stippled woolly appearance. The metaphyseal regions were longer but not so splayed out as in typical rickets, nor was

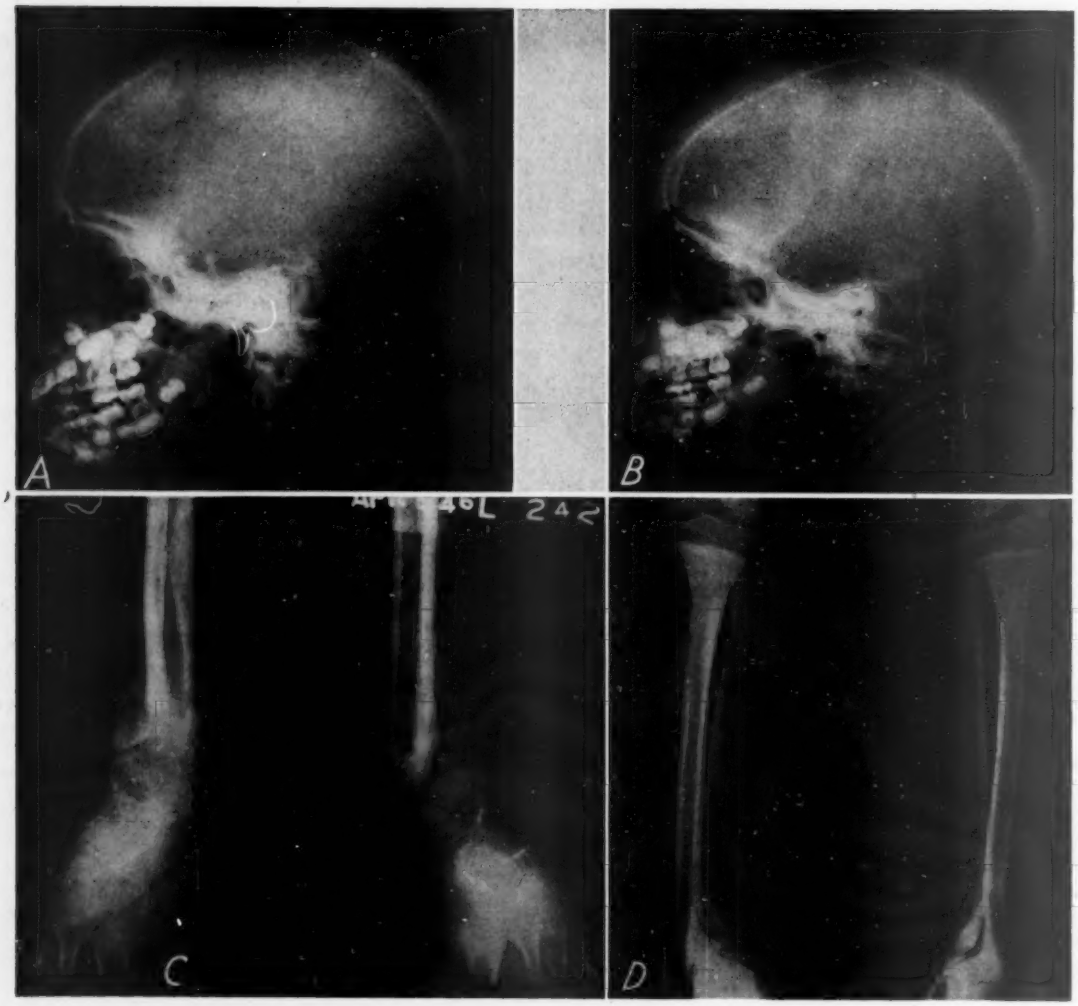

FIG. 3. *A*, skull in April, 1946, showed marked thickening of the cortex and a peculiar stippling of the bones of the vault. *B*, the skull in March, 1947, had a cortex which was still thickened. However, the stippled areas had given way to a more homogeneous radiolucent type of bone, with a few rounded areas of bony condensation scattered throughout the vault. *C*, the ankles in April, 1946, were markedly deformed, and there was a characteristic woolly appearance of the lower tibias and fibulas. *D*, in March, 1947, the ankles were still deformed; however, the distal ends of the tibias and fibulas showed a normal bony structure.

there any evidence of cupping. These changes were also noted at the distal ends of both radii and ulnas. Similar appearances were seen in the region of the femoral necks bilaterally, and the distal ends of both femurs (more marked on the right). The characteristic woolly changes were also noticed at the distal ends of both tibias and fibulas. All the bony changes were associated with deformities of varying degree in the affected areas.

Since the roentgenographic findings were so similar to those reported in renal rickets, the functional capacity of the kidneys was investigated. Over the entire period of months of observation the urine was always within normal limits. Azotemia was absent, and the blood nonprotein nitrogen and urea were normal. Urine concentration and phenolsulfonphthalein tests were normal, and intravenous pyelography revealed nothing of note. Further blood chemistry studies revealed a constantly normal calcium, and a relatively high phosphorus which rose temporarily and gradually fell toward normal. The most significant finding was a very high alkaline phosphatase which gradually fell toward normal as the patient's condition im-

proved. At one time the alkaline phosphatase reached a level of 108 Bodansky units. According to Jaffe and Bodansky only severe rickets and osteitis deformans can produce so high a level. The blood chemistry findings are given in Table 1.

TABLE I

Date	Blood Calcium	Blood Phosphorus	Alkaline Phosphatase in Bodansky Units
	mg. per 100 cc.	mg. per 100 cc.	
Apr. 12, 1946	9.9	6.0	—
Apr. 26, 1946	9.6	6.9	—
May 26, 1946	11.2	6.6	91.2
June 5, 1946	10.3	6.6	58.8
June 12, 1946	10.0	6.8	95.2
June 17, 1946	10.9	7.0	105.0
June 24, 1946	10.9	7.0	108.0
July 1, 1946	10.8	8.2	—
July 7, 1946	—	5.8	96.2
July 15, 1946	10.5	—	—
Aug. 14, 1946	10.8	7.8	73.2
Sept. 12, 1946	10.9	8.5	79.5
Oct. 31, 1946	—	7.3	49.1
Jan. 15, 1947	10.0	6.8	27.8
Feb. 11, 1947	10.8	6.8	22.8
Mar. 25, 1947	10.2	4.9	28.1

Under antirachitic therapy there was a gradual physical and mental improvement. In a few months the patient began to walk with some difficulty. The only interruption occurred at the end of 1946, when she had an attack of measles with an uneventful recovery. By February, 1947, the patient weighed 59 pounds and had attained a height of 46 inches.

Roentgenological examinations were carried out nearly every month. There was a gradual increase in the calcium deposits in the metaphyseal regions, and slight straightening of the deformities, especially at the knees, was noted. There was also a disappearance of the generalized stippling which was observed in the skull on admission.

Repeated roentgen examinations in March, 1947, showed the following: The thickening of the cranial vault and the widening of the diploe remained unchanged. However, the fine diffuse stippling had been replaced to a great extent by a more homogeneous radiolucent type of bone with a few rounded areas of bony condensation as seen in osteitis deformans. The metaphyseal ends of the long bones, i.e., the proximal humeri, the distal radii and ulnas, the necks and distal metaphyses of the femurs, the metaphyses for the proximal tibias, and the distal tibial and fibular metaphyses bilaterally appeared to be almost completely filled in with calcified osseous tissue. There were some slight improvement in the bony deformities at all the affected joints.

CONCLUSION

An atypical case of rickets in a seven year old colored female is presented. On admission roentgenographic examination of the patient showed all the bone changes found in the woolly type of infantile dwarfism, which Teall and Parsons claim is pathognomonic of renal rickets. Yet clinically the patient showed a high blood alkaline phosphatase and the physical signs of rickets. There was no evidence of kidney involvement. Finally, the child showed marked improvement clinically, through a lowering of the alkaline phosphatase, and on roentgen examination of the bony structures, after being placed on an antirachitic regimen.

The authors are indebted to Mr. Frank L. Scudero for his blood chemistry determinations, and to Dr. James R. Lisa of the Department of Pathology, City Hospital, for his valuable suggestions in the preparation of this paper.

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PAROSTEAL OSTEOID CHONDROMA

By FELIX LEESER, M.D.
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DOUBTLESS in cases of suspected bone tumors the greatest responsibility for the diagnosis will be placed upon the roentgenologist from the beginning. From him the clinician expects a statement on the extent and underlying pathology. The value of his verdict is proportional to his experience, which should have taught him to be very critical and to collaborate closely with the clinician and pathologist. Only in big places is it possible for an exchange of ideas to take place by actual discussion, therefore the evaluation of observation must suffer in the smaller hospitals. Moreover such cases as are not met with in daily practice are difficult and give cause for speculation in diagnosis. The evaluation of such cases being of great value, it is thought to be of sufficient interest to warrant the full report of one observation.

CASE REPORT

The patient, R.S., was a boy, aged five years; seen by the doctor on January 7, 1944. History of trauma with swelling in region of left medial malleolus. Anorexia.

Roentgenograms of the left ankle, anteroposterior and lateral views, were taken on January 10, 1944. The anteroposterior view shows a well defined dense shadow with clearly marked trabeculation situated in the soft tissues at the medial aspect of astragalus. There does not appear to be any connection between this shadow and astragalus, the surface of which exhibits some irregular outlines at this side. Marked swelling of the surrounding soft tissues. Diagnosis: Probably benign tumor. ?Osteofibroma. Traumatic osteoma and osteochondroma unlikely (Fig. 1).

January 24, 1944. Removal of bony growth from medial aspect of left talus—shelled out quite well. Wound closed in layers. Specimens sent to Dr. Duhlig.

January 29, 1944. Pathological report: Benign osteoma.

March 17, 1944. Recurrent swelling noted. Severe lump over wound. Swelling softer than previously. In spite of conservative treatment, swelling gradually increased, no tenderness.

September 6, 1944. Another roentgen examination reveals recurrence of the lesion almost to the same extent and configuration. The swelling of the soft tissues appears to be more advanced. Slight irregularity of medial aspect of talus. A connection between talus and tumor is not definitely recognizable on account of partial superimposing of the shadows (Fig. 2).

September 16, 1944. Recurrent bony tumor removed from same region as previously. Again

FIG. 1. Demonstration of tumor shadow in anteroposterior and lateral views before operation.

FIG. 2. Recurrence of the tumor almost to the same extent and configuration. Roentgenograms taken about eight months after operation.

tumor shelled out well. Roentgen examination made on completion of operation in theatre revealed a fairly dense, homogeneous opacity on a level with the ankle joint. The dense tumor shadow is no longer recognizable (Fig. 3). Specimen sent to Dr. Canny.

October 23, 1944. Pathological report: "There is no histological evidence of a neoplastic lesion but rather a disorder of growth. The peripheral compact bone is thinned almost to the point of extinction but is partly replaced by islets of cartilage which seem to have developed from the periosteum. Rarefaction of the cancellous bone has occurred and small islets of aberrant cartilage are present in some of the bony trabeculae. Although one small focal accumulation of lymphocytes is to be seen in the intertrabecular

Fig. 3. Roentgenogram taken immediately upon completion of second operation. The dense shadow is no longer recognizable. Some opacity remains in the region of the tumor.

connective tissue—which is chiefly fatty—this is not to be regarded as indicative of inflammation, as such foci occur in a number of bony dysplasias. No condition exactly comparable with this has, as far as I am aware, been described. In some respects it resembles the 'Fi-

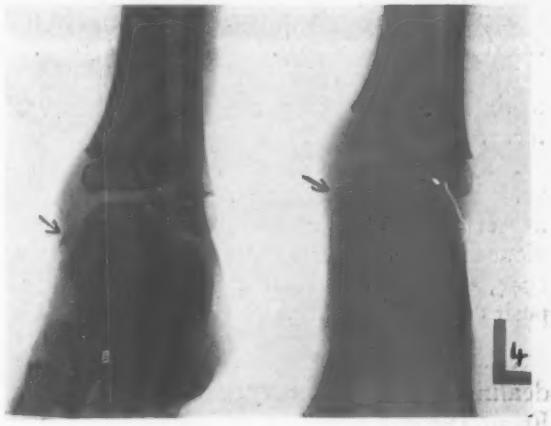

Fig. 4. Control roentgenograms taken about nine months after the second operation. No evidence of recurrence. Dense linear shadow at medial aspect of talus indicated by arrow.

brous Dysplasia of Bone' described by Lichenstein and Jaffe (*Arch. Path.*, 1942, *33*, 777–816), but differs from this in the absence of true fibrosis of the intertrabecular connective tissue. We have had one case presenting a similar histopathological picture. In this instance the ilium and femur were involved. Both lesions were diagnosed roentgenographically as chondromata, but whereas bulky deposits of cartilage were found at operation in the ilium when progressive destruction of the distal third of the femur finally led to the amputation, there was no tumor but on the contrary a great rarefaction of the bony tissue with the same focal development of miscroscopic islets of cartilage that characterizes the lesion in this case. These dysplastic lesions of bone often involve more than one bone but are frequently unilateral. It would be of interest to investigate this patient's skeleton now, and at intervals of perhaps six months, to see if any other foci of disordered growth develop. The fibrous dysplasia to which the condition we are now considering seems to be related is thought to have an endocrine basis, as it is often associated with precocity of physical development, skin pigmentation and sometimes with hyperthyroidism. While one can exclude neoplasia even of a benign character in this case, there may well be a progressive extension of the lesion locally which may eventually call for amputation. This should not be lightly undertaken unless the mechanical disability is severe, as the disease may be self limiting, though on this point we have no certain knowledge—at

least there is no evidence that the dysplasias ever pass into neoplasia (except of course in the case of Paget's disease)."

The patient was seen by his doctor from time to time after second operation. No evidence of recurrence.

May 29, 1945. Control roentgenogram revealed a small dense linear shadow at medial aspect of talus, which was not present on previous examination carried out on September 16, 1944, suggesting periosteal thickening or deposit of lime in the capsule (Fig. 4).

Comment. We are here without doubt dealing with a rarer type of observation. From the start it was apparent roentgenologically that we were dealing with a benign tumor, probably of heterogeneous histopathology. At any rate the roentgen diagnosis between a real tumor and any kind of new bone formation had to be taken with reserve. The first pathological examination suggested benign osteoma—probably owing to examination of only a part of the tumor. Recurrence after removal is not necessarily proof of malignancy in cases where a microscopic projection of the tumor has been left behind or where the tumor was multilocular from the beginning. However, at the operation the tumor was easily removed, and the recurrence proved to be only a secondary metaplasia of the matrix probably incompletely removed at the first operation. The second pathological examination confirmed chondromatous changes in the tumor, probably originating in the periosteum, with displaced islets of chondroblastic elements. Therefore we are dealing with a localized overgrowth of cartilage with secondary changes of calcification and ossification by production of bone in a cartilaginous matrix. In the etiology only two factors are worth considering: a congenital disturbance in the development of the cartilaginous elements or with more probability trauma. Ewing states that in solitary chondroma the possibility of traumatic origin must be admitted. When one has evaluated and analyzed critically the pathology one is forced to the conclusion that the whole process is one of osteoid chondroma. Virchow first described an osteoid chondroma developing from the periosteum of the long bones. Such tumors are not known to me to arise in short bones. The process has a certain similarity to parosteal spongiotic osteoma, which is sometimes hard to differentiate from a localized myositis ossificans. The differential diagnosis may be discussed briefly. In the early stages capsular osteoma and mono-articular osteogenic sarcoma must be excluded. Obviously great difficulty can arise only in the beginning, making a positive diagnosis almost impossible. Further follow up examinations should be able to clarify the nature of the condition and differentiate it from osteoid chondroma.

SUMMARY

A case of parosteal osteoid chondroma with clinical, roentgenological and pathological examinations is described. The etiology and differential diagnosis are briefly discussed.

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AMPLIFICATION OF THE FLUOROSCOPIC IMAGE*

BY MEANS OF A THICK DENSE CLEAR CRYSTALLINE DETECTOR SCREEN AND A SCANNING ROENTGEN-RAY TUBE

(Right to reproduce in whole or in part expressly granted to the United States Government)

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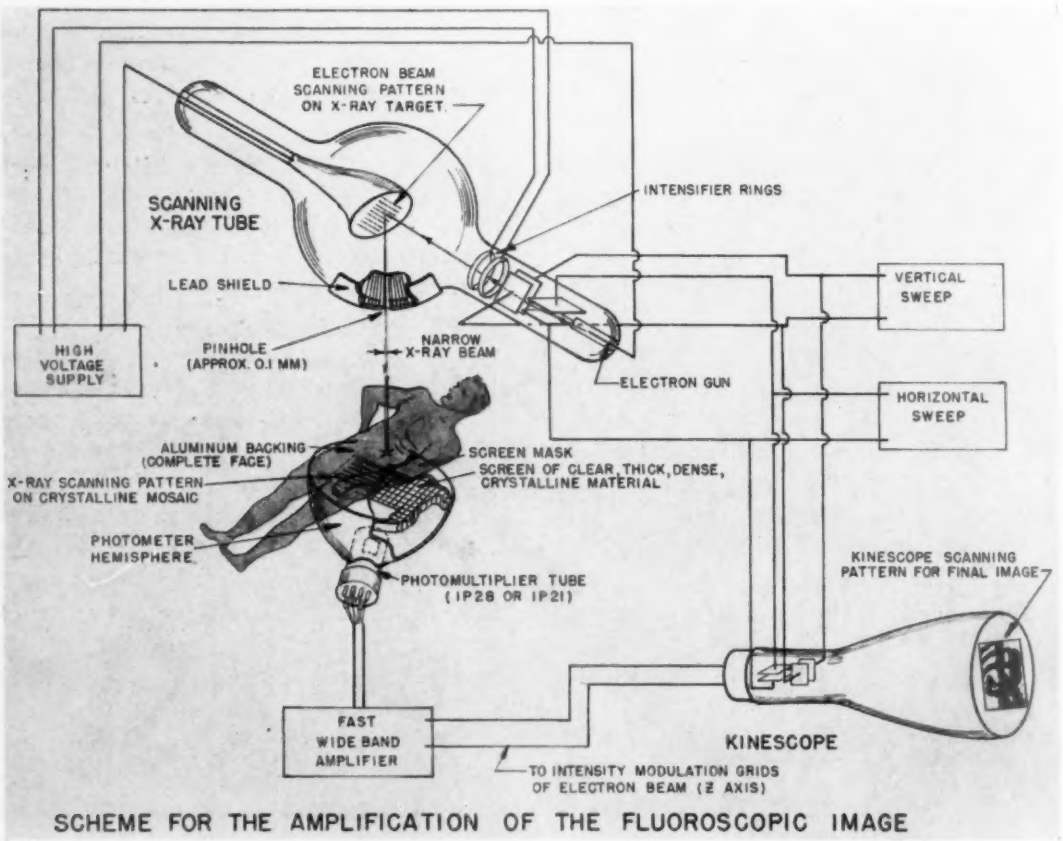
ON SEVERAL occasions Dr. Paul C. Hodges† has emphasized the need for roentgenologic equipment which will operate on a much smaller dose-rate for the patient than is used at present in fluoroscopy and at the same time will yield an equally brilliant or even more brilliant image which in some fashion or other results from the passage of roentgen rays through the patient. Such a result might be realized by the method which is depicted in Figure 1. In essence, a scanning roentgen-ray tube generates a scanning roentgen-ray beam which after passage through the



SCHEME FOR THE AMPLIFICATION OF THE FLUOROSCOPIC IMAGE

FIG. 1

* This work has been supported in part by a grant from the Wallace O. and Clara A. Abbott Fund of the University of Chicago and in part by a Navy Research Grant.

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patient falls upon a clear dense crystalline fluorescent screen. Here the roentgen rays produce visible or near visible light quanta which in turn create a photoelectric current which is amplified and subsequently used to modulate the magnitude of an electron beam current in a kinescope. Thus the intensity of the fluorescent spot on the face of the kinescope at a given instant will be proportional to the intensity of the bundle of roentgen rays which strike the crystalline screen after transit through the patient at a spot which corresponds to the position of the roentgen-ray beam at that particular time. Now since the electron beam in the roentgen-ray tube and the electron beam in the kinescope are both driven by the same sweep circuits a roentgen shadow image will be reconstructed on the kinescope screen. Thus the observer may examine the picture on the kinescope without being exposed to roentgen rays, and if two kinescope tubes are used the image may be monitored on one and a photograph can be taken at any desired time on the other.

The success of such a scheme depends upon these main factors: (1) the intensity and sharpness of the roentgen-ray scanning beam; (2) the magnitude of the photoelectric current generated for a single picture element in comparison to the statistical fluctuations of that current, and (3) the amount of background effects. In the following paragraphs the various dimensions which are given are rough estimates that are compatible with reasonable values for these conditions.

The scanning roentgen-ray tube would consist of a high intensity electron gun capable of forming a fine focal spot of the order of 0.1 mm. to 1 mm. in diameter at the target and with a beam current of the order of 100 milliamperes. A means must be provided for deflecting the beam back and forth and up and down so that it will describe a usual type rectangular scanning pattern on the target. Electrostatic deflection plates are shown in Figure 1; however, electromagnetic deflection might prove more satisfactory. Intensifier rings might be employed not only to produce a graded electric field but also to aid in focussing the beam. The necessary target size would be determined by the area of the scanning pattern which is simply the area to be examined roentgenologically multiplied by the ratio of the target to pinhole distance to the pinhole to screen distance. The ratio would probably be between one-half to one-fifth.

Several materials which exist in large transparent crystals and fluoresce under roentgen radiation are suitable for the fluorescent screen of the detector. The principal ones[1] are scheelite ($CaWO_4$), calcium fluoride (CaF_2), synthetic sapphire (Al_2O_3), spodumene ($LiAlSi_2O_6$), lithium fluoride, and naphthalene, and other homologues of benzene. Calcium tungstate ($CaWO_4$) is the best in many respects. With a density of 6 grams per cubic centimeter, of which over 60 per cent is tungsten, it yields many photoelectrons and Compton electrons per unit volume which in turn excite fluorescent radiation which is mainly in the visible and ultraviolet. It appears to be quite transparent to its fluorescent radiation. The crystals can be cut and polished into rectangular blocks which then can be lapped along the edges and fitted into a mosaic of a given thickness and then cemented to a thin aluminum backing. This screen is then placed in the unmasked region of the equatorial plane of the photometer hemisphere which serves to collect the fluorescent radiation of the screen for the photocell.

It has been found that when large $CaWO_4$ crystals are excited by a single gamma ray from radium the rise time of the resultant pulse of light is less than 2×10^{-7} second (this was the limit of resolution of the wide-band amplifier) and in addition the pulse was completely over in less than 1.5×10^{-6} second. Also no phosphorescence was observed in $CaWO_4$ at $-80°$ C. This high speed occurrence and decay of the scintillation is important in order to be able to

[1] From a letter to the Editor of the *Physical Review* submitted March 25, 1948, by the author.

use a small scanning spot with a high scanning speed for picture detail and short exposures. For example, suppose in some preliminary work that a scanning spot of 1 square millimeter area was used to scan a patient area of $4\frac{1}{4} \times 7$ inches or approximately 20,000 square millimeters. If one complete scan were done in one-twentieth of a second then each square millimeter of area of the screen would be visited by the roentgen rays for a period of 2.5×10^{-6} second. Thus the fluorescent material must emit its radiation and cease before the roentgen-ray beam arrives at the adjacent picture spot i.e. in 2.5×10^{-6} second. It is worth while to note, too, that if the intensity of the roentgen rays were sufficient to yield a photograph of the same area by the usual photofluoroscopy method the average intensity over this same area in the scanning method is only one-twenty thousandth as great. If this intensity does not give a decent signal-to-noise ratio at the output of the phototube the intensity of the roentgen rays may be increased by a factor of nearly a hundred in order to improve the picture.

A crystalline calcium tungstate screen 3 mm. thick (approximately 1 cm. square) was prepared and placed in front of the photocathode of a 1P28 photomultiplier tube[2] and cooled with solid CO_2. This detector was placed within a lead house. The crystal was irradiated with roentgen rays from a small Waite Portable X-ray Unit. These roentgen rays passed through a hole 1 mm. in diameter in the side of the lead house. This aperture was 60 cm. from the target of the roentgen-ray tube and 13 cm. from the crystal. At the peak of the alternating current voltage across the roentgen-ray tube the peak current (as estimated from the average) was 30 ma. and a tube voltage near 80,000 volts. This yielded at the same instant a voltage of 300 millivolts across the 10,000 Ω resistor of the photomultiplier tube and a peak noise fluctuation of ±5 per cent. No delayed pulses were observable on the cathode-ray oscillograph.

A sample of a fluorescent screen used in photofluoroscopy was put in place of the 3 mm. $CaWO_4$ screen. The output voltage of the photomultiplier tube with this screen was less than half that obtained with the 3 mm. $CaWO_4$ screen. Delayed pulses existed up to sixty seconds after a one second exposure through the aperture and were in excess of 2,500 per second for the first ten seconds. Such a screen would be unsuitable for scanning in the above type of roentgenologic work.

These preliminary experiments seem to indicate the feasibility of utilizing apertures smaller than one millimeter in diameter and still maintaining a good signal-to-noise ratio. In addition it should be reasonable to expect to use a tube current of 100 ma. The main problem still to be answered by experiment is how much noise due mainly to statistical fluctuations can be tolerated in the picture without loss of detail.

[2] 10,000 Ω anode resistor, 100 volts per dynode, 180 volts between dynode 9 and anode.

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EDITORIAL

RADIANT ENERGY INJURIES

THREE years have now elapsed since massive atomic energies were suddenly released over Hiroshima and Nagasaki. The effects of these energies have since then been studied assiduously from many angles. In particular, some very valuable observations have been made on the medical aspect of the problem.

In considering the general biologic activity of the energies produced by the atom, the main role must be attributed to the specific ionization of the different types of radiations. During a sudden explosion radiant energy is emitted which extends over a rather wide range of the spectrum, from the infrared through the visible light and ultraviolet rays down to the most penetrating roentgen and gamma rays. In addition electrons, neutrons and various radioactive fission products are liberated. The effects of the air blast and pressure shock are the same as in any other explosion except that there is a difference in degree and extent.

An atomic bomb, when exploded in mid-air, sends four successive waves. The first to reach the ground travels with the speed of light and includes the various components of the electromagnetic spectrum; the second contains myriads of atomic particles and fission products; the third is the shock wave which travels with the speed of sound, and the fourth is the blast wave, following immediately after the shock wave.

At Hiroshima and Nagasaki the atomic bombs were detonated at such an altitude that a major part of the fission products rapidly rose to the stratosphere. Therefore most of the biologic damage came from the heat, the radiant energies and above all from the gamma rays. Larkin,[1] in studying the distribution of the radiation in Nagasaki, divided the area of destruction into five zones: Zone 1, which extended from the center of the explosion to a distance of 1,000 meters, was called the lethal zone, as there were very few survivors there; Zone 2, which extended from 1,000 to 1,250 meters, was the zone where survivors showed maximum radiation effects; Zone 3 extended from 1,250 to 1,500 meters; Zone 4 from 1,500 to 1,750 meters and Zone 5 beyond 1,750 meters. In the last three zones severe superficial burns, but practically no immediate radiation effects, were found. The gamma-ray emission corresponded on the ground to a dose of the order of 1,000 roentgens at 1,000 meter distance from the center of explosion, and 10 r at 3,000 meters.

The injurious effects resulting from the explosion of an atomic bomb may be placed in two main groups. The first includes the immediate injuries which may range from sudden death in Zone 1, to severe reaction in Zone 2 and no noticeable effect in Zone 5. The second group contains the late changes and especially the more or less permanent sequelae which have resulted over a period of years. Eventually a third group may be added, including the genetic changes, but it may be one or several generations before such changes can be properly evaluated.

The immediate injuries which are produced by the sudden release of large atomic energies were studied by a number of investigators. In general, the sequence of events may be divided into three stages.

The first stage was over in a few minutes or hours at the most. According to Larkin, in Zone 1 it led to practically 100 per cent mortality and there were many deaths in the adjacent zones. The very few who sur-

[1] Larkin, J. C. Distribution of radiation in the atomic bombing of Nagasaki. AM. J. ROENTGENOL. & RAD. THERAPY, 1946, *55*, 525–532.

vived in Zone 1 were protected by concrete, bridge or similar structure. Although most of these victims also suffered from burns and the blast effect, they were exposed to sufficient gamma-ray intensity to be killed. Shock and severe radiation sickness were prominent features of the disease in those who survived in the lethal areas and accounted for the largest percentage of deaths during the first week.

The second stage started ten to fourteen days after the explosion. It was characterized by epilation, diarrhea, fever and a progressive blood change. According to Larkin, the epilation was almost completely confined to persons in Zones 2 and 3. In the outer zones epilation was uncommon and the degree was also less. The severity of the other symptoms likewise depended on the amount of the radiation that the patient had received. According to LeRoy[2] the heavily exposed patients usually had diarrhea and fever on the day after the bombing, as part of the radiation sickness. Others developed diarrhea later due to ulceration that occurred throughout the bowel. Fever always constituted a serious complication, rising as high as 106° F. If it remained steady and high it indicated poor prognosis. The blood changes followed the pattern so well known from our experience with roentgen or gamma irradiation. LeRoy, in summarizing the observations made at Nagasaki and Hiroshima, states that the two major phenomena which endangered life in this stage were the gastrointestinal disturbances and the destruction of the hemopoietic tissues. The intense diarrhea and vomiting led to dehydration and acidosis, being in many instances the sole contributory cause of death. The damage to the bone marrow was characterized by severe leukopenia, which persisted for a period of one to three weeks, often greatly reducing the patient's capacity to resist infection. In the hemorrhagic state there was bleeding from the gums, from the ulcerated mucosae and from the wounds associated with marked thrombocytopenia. Fatal hemorrhages occurred in the central nervous system, the myocardium and adrenal glands. Larkin found that the greatest number of persons afflicted with blood changes died at the end of the seventh week.

The third stage was dominated by processes of recovery. The blood counts according to Larkin reached a maximum depression near the twenty-eighth day when in patients of Zone 2 the average leukocyte count dropped to 980, the lowest being 514. In Zone 3 the average was 3,750, with a low of 1,000 and several normal counts. Beyond Zone 3 the average white blood cell count was 4,780. After the twenty-eighth day the blood count gradually returned to normal. Some investigators found that at times there was a temporary increase of the white blood cell count above the normal level. In this stage the burns likewise healed, leaving rather thick keloids, and the patients as a whole regained their former health. The time of recovery varied from a few weeks to many months. Since blood disorders often lasted much longer than would be expected from similar observations with roentgen rays the theory was advanced that perhaps the extremely penetrating gamma rays may have induced some radioactivity in the victims' bones leading to the emission of beta particles which in turn would temporarily depress the bone marrow. In this stage an effect on the reproductive organs was also observed. Men became sterile, women stopped menstruating, and in the pregnant, miscarriages occurred not infrequently. In studying the problem of amenorrhea Larkin found that in Zone 2 this occurred almost routinely but there were some scattered cases also in the other zones.

The information concerning the late injuries and other medical sequelae resulting from the sudden release of massive atomic energies is still rather incomplete. In April,

[2] LeRoy, G. V. The medical sequelae of the atomic bomb explosion. *J.A.M.A.*, 1947, *134*, 1143–1148. This article is an abstract of a report of the Joint Commission for the Investigation of the Effects of the Atomic Bomb in Japan.

1947, the Office of the Surgeon General of the Army published a report of the Atomic Bomb Casualty Commission[3] which began a six weeks' investigation in Japan from late November, 1946, to early January, 1947. Thus this report surveys the situation as it existed almost one and a half years after the bombing. Several observations made are of great interest.

In view of the conflicting figures on the number and type of casualties the exact status was determined through the cooperation of Professor Masao Tsuzuki of the Tokyo Imperial University. The Hiroshima prefecture listed, nineteen days after the explosion, 46,185 persons as dead, 17,429 as missing, 19,691 as severely injured, 44,979 as slightly injured and 235,656 as suffering from other diseases. In other words, the number of dead and missing amounted to 63,614. Six months after the catastrophe the toll of dead and missing stood at 92,133 excluding the military dead. In Nagasaki the toll was 23,753 dead, 1,924 missing, 23,345 wounded, and 89,025 other sufferers. A study of the sex incidence showed that the distribution was equal outside of a radius of 1,500 meters from the ground center, but within the radius of 1,000 meters, that is in Zone 1, more women survived than men. Apparently under identical conditions women are more resistant than men.

An investigation of the sterility of males was carried out three to four months after the bombing in Hiroshima. A series of 124 males were examined by counting the number of spermatocytes in the ejaculated sperm. According to the report of the Commission a reduced number of spermatocytes was even observed within a radius of 3,000 meters from the ground center, whereas within a radius of 1,500 meters, corresponding to the three inner zones, fully one-half of the cases showed sterility.

Another observation which impressed the Commission very much was the fact that many of the burns healed with large keloids. The maximum growth of such tissue was reached within eight to ten months following the injury. In a later publication Warren[4] pays considerable attention to these keloids. He states that Captain Melvin A. Block, in cooperation with a group of Japanese scientists, made an intensive investigation of the keloids due to the atomic bomb and compared them with those produced in scars of burns from incendiary and other sources. The fact that frequently only a portion of a given scar showed true keloid would seem to rule out the individual reaction as the causative agent. On the other hand, there was no definite evidence linking the occurrence of keloid specifically to an atomic energy exposure. Perhaps the severe infections which always complicated the second degree and third degree burns may have played a part in their production. So far, no malignant degeneration of the keloid tissue has been observed in a single case.

Likewise no instance of true skin tumor, or tumor of any other location has been encountered. As is known, there is a steadily growing literature to the effect that ionizing radiations may exhibit, under certain circumstances, cancerogenic properties in animals. There is also some evidence that cutaneous carcinoma, osteogenic sarcoma and fibrosarcoma may occur in man following prolonged exposure to irradiation.

As mentioned above, a rather large percentage of the survivors at Hiroshima and Nagasaki showed blood changes of varying degrees immediately after the bombing. Warren found that nearly two years later most of the patients had returned approximately to normal. Three cases of leukemia, one probable case of leukemia and of multiple myeloma were noted. This incidence, however, seems to correspond to the general incidence of leukemia as given by the United States Bureau of Census and the Metropolitan Life Insurance Company.

Obviously, further observations over a

[3] Salient points in report of Atomic Bomb Casualty Commission. Release from the Office of the Surgeon General of the Army, April, 1947. *Military Surgeon*, 1947, *100*, 518–521.

[4] Warren, Shields. The Nagasaki survivors as seen in 1947. *Military Surgeon*, 1948, *102*, 98–100.

long period of time are necessary before the entire picture can be fully evaluated. The Atomic Bomb Casualty Commission expresses the view that "from previous irradiation experiences with both animals and human beings, there is good reason to believe that reproductive disturbances, malignancies of one form or another, shortened life span, altered genetic pattern, etc. will in time appear in greater or lesser degrees." For a comprehensive study of all these possibilities it is planned to maintains, in cooperation with Japanese scientists, a continuing check of the populations of Hiroshima and Nagasaki.

T. Leucutia

PROF. DR. MED. LEOPOLD KÜPFERLE

WITH regret the Journal announces the death of Prof. Dr. Med. Leopold Küpferle of the University of Freiburg, Germany. Professor Küpferle was an outstanding radiologist and was elected to honorary membership in the American Roentgen Ray Society in 1930. According to the brief information recently received, he died on November 27, 1944, in his hospital during an air attack when he left the air raid shelter to assist a suffering patient.

SOCIETY PROCEEDINGS, CORRESPONDENCE AND NEWS ITEMS

Items for this section solicited promptly after the events to which they refer

MEETINGS OF ROENTGEN SOCIETIES*

UNITED STATES OF AMERICA

AMERICAN ROENTGEN RAY SOCIETY
Secretary, Dr. H. Dabney Kerr, University Hospital, Iowa City, Iowa. Annual meeting: Palmer House, Chicago, Ill., Sept. 14–17, 1948.

AMERICAN RADIUM SOCIETY
Secretary, Dr. H. F. Hare, 605 Commonwealth Ave., Boston, Mass. Annual meeting: Stevens Hotel, Chicago, Ill., June 20–22, 1948.

RADIOLOGICAL SOCIETY OF NORTH AMERICA
Secretary, Dr. D. S. Childs, 607 Medical Arts Bldg., Syracuse, N. Y. Annual meeting: Hotels Fairmont and Mark Hopkins. San Francisco, Calif., Dec. 5–10, 1948.

AMERICAN COLLEGE OF RADIOLOGY
Secretary, Mac F. Cahal, 20 N. Wacker Drive, Chicago 6. Annual meeting: Sheraton Hotel, Chicago Ill., June 20, 1948.

SECTION ON RADIOLOGY, AMERICAN MEDICAL ASSOCIATION
Secretary, Dr. U. V. Portmann, Cleveland Clinic, Cleveland, Ohio. Annual Meeting: Chicago, Ill., June 21–25, 1948.

ALABAMA RADIOLOGICAL SOCIETY
Secretary, Dr. C. S. Stickley, 515 Bell Bldg., Montgomery, Ala. Next meeting time and place of Alabama State Medical Association.

ARKANSAS RADIOLOGICAL SOCIETY
Secretary, Dr. Fred Hames, 511 National Bldg., Pine Bluff, Ark. Meets every three months and also at time and place of State Medical Association.

BROOKLYN ROENTGEN RAY SOCIETY
Secretary, Dr. A. H. Levy, 1354 Carroll St., Brooklyn 13, N. Y. Meets monthly on fourth Tuesday, October to April.

BUFFALO RADIOLOGICAL SOCIETY
Secretary, Dr. Mario C. Gian, 610 Niagara St., Buffalo, N. Y. Meets second Monday evening each month, October to May inclusive.

CENTRAL NEW YORK ROENTGEN RAY SOCIETY
Secretary, Dr. Dwight V. Needham, 608 E. Genesee St., Syracuse, N. Y. Three meetings a year January, May, November.

CHICAGO ROENTGEN SOCIETY
Secretary, Dr. T. J. Wachowski, 310 Ellis Ave., Wheaton, Ill. Meets second Thursday of each month October to April inclusive at the Palmer House.

CINCINNATI RADIOLOGICAL SOCIETY
Secretary, Dr. Eugene L. Saenger, 735 Doctors Bldg., Cincinnati 2, Ohio. Meets last Monday of each month, September to May, inclusive.

CLEVELAND RADIOLOGICAL SOCIETY
Secretary, Dr. George L. Sackett, 10515 Carnegie Ave. Cleveland 6, Ohio. Meetings at 6:30 P.M. on fourth Monday of each month from October to April.

DALLAS-FORT WORTH ROENTGEN STUDY CLUB
Secretary, Dr. X. R. Hyde, Medical Arts Bldg., Fort Worth, Texas. Meets in Dallas on odd months and in Fort Worth on even months, on third Monday, 7:30 P.M.

DENVER RADIOLOGICAL CLUB
Secretary, Dr. Mark S. Donovan, 306 Majestic Bldg., Denver 2, Colo. Meets third Friday of each month at Department of Radiology, Colorado School of Medicine.

DETROIT ROENTGEN RAY AND RADIUM SOCIETY
Secretary, Dr. E. R. Witwer, Harper Hospital. Meets monthly on first Thursday from October to May, at Wayne County Medical Society Building.

FLORIDA RADIOLOGICAL SOCIETY
Secretary, Dr. J. A. Beals, St. Luke's Hospital, Jacksonville, Fla. Meets twice yearly, in April preceding annual meeting of Florida Medical Society, and in November.

GEORGIA RADIOLOGICAL SOCIETY
Secretary, Dr. Robert Drane, DeRenne Apartments, Savannah, Ga. Meets in mid-winter and at annual meeting of Medical Association of Georgia in the spring.

HOUSTON X-RAY CLUB
Secretary, Dr. Curtis H. Burge, 3020 San Jacinto St., Houston 4, Texas. Meets fourth Monday each month.

RADIOLOGICAL SOCIETY OF KANSAS CITY
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

ILLINOIS RADIOLOGICAL SOCIETY
Secretary, Dr. Wm. DeHollander, St. John's Hospital, Springfield, Ill. Meets three times a year.

INDIANA ROENTGEN SOCIETY
Secretary, Dr. J. A. Campbell, Indiana University Hospitals, Indianapolis 7. Meets second Sunday in May.

IOWA X-RAY CLUB
Secretary, Dr. Arthur W. Erskine, 326 Higley Bldg., Cedar Rapids, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. Special meetings by announcement.

KANSAS RADIOLOGICAL SOCIETY
Secretary, Dr. Anthony F. Rossitto, Wichita Hospital, Wichita, Kansas. Meets annually with the State Medical Society.

KENTUCKY RADIOLOGICAL SOCIETY
Secretary, Dr. W. C. Martin, 321 W. Broadway, Louisville. Meets annually in Louisville on first Saturday in Apr.

LONG ISLAND RADIOLOGICAL SOCIETY
Secretary, Dr. Marcus Wiener, 1430-48th St., Brooklyn, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

LOS ANGELES RADIOLOGICAL SOCIETY
Secretary, Dr. Moris Horwitz, 441 No. Camden Drive, Beverly Hills, Calif. Meets second Wednesday each month at Los Angeles County Medical Assn. Building.

LOUISIANA RADIOLOGICAL SOCIETY
Secretary, Dr. J. R. Anderson, 1130 Louisiana Ave., Shreveport. Meets annually during Louisiana State Medical Society Meeting.

LOUISVILLE RADIOLOGICAL SOCIETY
Secretary, Dr. E. L. Pirkey, Louisville General Hospital, Louisville 2, Ky. Meets monthly on second Friday at Louisville General Hospital.

MICHIGAN ASSOCIATION OF ROENTGENOLOGISTS
Secretary, Dr. R. D. McDuff, 220 Genesee Bank Bldg., Flint 3, Mich.

MILWAUKEE ROENTGEN RAY SOCIETY
Secretary, Dr. C. A. H. Fortier, 231 W. Wisconsin Ave., Milwaukee, Wis. Meets monthly on second Monday at University Club.

* Secretaries of societies not here listed are requested to send the necessary information to the Editor.

Minnesota Radiological Society
Secretary, Dr. Chauncey N. Borman, 802 Medical Arts Bldg., Minneapolis 2, Minn. Two meetings yearly, one at time of Minnesota State Medical Association the other in the fall.

Nebraska Radiological Society
Secretary, Dr. Ralph C. Moore, Nebraska Methodist Hospital, Omaha 3, Nebr. Meets third Wednesday of each month, at 6 P.M. at either Omaha or Lincoln.

New England Roentgen Ray Society
Secretary, Dr. George Levene, Massachusetts Memorial Hospitals, Boston, Mass. Meets monthly on third Friday, Boston Medical Library.

New Hampshire Roentgen Ray Society
Secretary, Dr. A. C. Johnston, Elliott Community Hospital, Keene, N. H. Meets four to six times yearly.

New York Roentgen Society
Secretary, Dr. Ramsay Spillman, 115 East 61st St., New York City. Meets monthly on third Monday, New York Academy of Medicine, at 8:30 P.M.

North Carolina Radiological Society
Secretary, Dr. J. E. Hemphill, 323 Professional Bldg., Charlotte 2, N. C. Meets in May and October.

North Dakota Radiglogical Society
Secretary, Dr. C. O. Heilman, 807 Broadway, Fargo. Meetings held by announcement.

Ohio State Radiological Society
Secretary, Dr. Carroll C. Dundon, 2065 Adelbert Road, Cleveland 6, Ohio. Next meeting at annual meeting of Ohio State Medical Association, Cincinnati, Ohio, March 31, 1948.

Oklahoma State Radiological Society
Secretary, Dr. P. E. Russo, 230 Osler Bldg., Oklahoma City, Okla. Three regular meetings annually.

Oregon Radiological Society
Secretary, Dr. William Y. Burton, 242 Medical Arts Bldg., Portland 5, Oregon. Meets monthly 2nd Wednesday, 8:00 P.M., Library of University of Oregon Medical School.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets first Tuesday of each month.

Pacific Northwest Radiological Society
Secretary, Dr. S. J. Hawley, 1320 Madison St., Seattle 4, Wash. Meets annually in May.

Pacific Roentgen Society
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco, Calif. Meets annually, during meeting of California Medical Association.

Pennsylvania Radiological Society
Secretary, Dr. J. M. Converse, 416 Pine St., Williamsport. Annual meeting, May 21–22, 1948, Erie, Pa., at Hotel Lawrence.

Philadelphia Roentgen Ray Society
Secretary, Dr. Arthur Finkelstein, Graduate Hospital, 19th and Lombard St. Meets first Thursday each month October to May, at 8:00 P.M., in Thomson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. R. P. Meader, 4002 Jenkins Arcade Pittsburgh 22, Pa. Meets 6:30 P.M. at Webster Hall Hotel on second Wednesday each month, October to May inclusive.

Queens Roentgen Ray Society
Secretary, Dr. J. E. Goldstein, 88-29 163rd St., Jamaica 3, N. Y. Meets fourth Monday of each month except during the summer.

Radiological Section, Baltimore Medical Society
Secretary, Dr. Harry A. Miller, 2452 Eutaw Place, Baltimore. Meets third Tuesday each month, September to May.

Radiological Section, Connecticut Medical Society
Secretary, Dr. Robert M. Lowman, Grace-New Haven Community Hospital, New Haven 11, Conn. Meets bimonthly on second Thursday, at place selected by Secretary.

Radiological Section, District of Columbia Medical Society
Secretary, Dr. A. A. J. Den, 1801 K St., N. W., Washington, D. C. Meets Medical Society Auditorium, third Thursday of January, March, May and October at 8:00 P.M.

Radiological Section, Southern Medical Association
Secretary, Dr. Roy G. Giles, Temple, Texas.

Radiological Society of New Jersey
Secretary, Dr. Raphael Pomeranz, 31 Lincoln Park, Newark, N. J. Meets annually at time and place of State Medical Society. Mid-year meetings at place chosen by president.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. Murray P. George, Strong Memorial Hospital. Meets monthly on third Monday from October to May, inclusive, 8 P.M. at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary, Dr. Maurice D. Frazer, 1037 Stuart Bldg., Lincoln, Nebr. Meets Salt Lake City, Utah, at Hotel Utah, Aug. 12, 13, 14, 1948.

St. Louis Society of Radiologists
Secretary, Dr. Edwin C. Ernst, Beaumont Medical Building, St. Louis, Mo. Meets fourth Wednesday of each month, except June, July, August, and September.

San Diego Roentgen Society
Secretary, Dr. R. F. Niehaus, 1831 Fourth Ave., San Diego, Calif. Meets monthly, first Wednesday at dinner.

Section on Radiology, California Medical Association
Secretary, Dr. D. R. MacColl, 2007 Wilshire Blvd., Los Angeles 5, Calif.

Section on Radiology, Illinois State Medical Society
Secretary, Dr. John H. Gilmore, 720 N. Michigan Ave., Chicago 11, Ill.

Shreveport Radiological Club
Secretary, Dr. R. W. Cooper, Charity Hospital, Shreveport, La. Meets monthly on third Wednesday, at 7:30 P.M., September to May inclusive.

South Carolina X-Ray Society
Secretary, Dr. T. A. Pitts, Baptist Hospital, Columbia, S. C. Meets in Charleston on first Thursday in November, also at the time and place of South Carolina State Medical Association.

Tennessee Radiological Society
Secretary, Dr. J. M. Frère, 707 Walnut St., Chattanooga, Tenn. Meets annually at the time and place of the Tennessee State Medical Association.

Texas Radiological Society
Secretary, Dr. R. P. O'Bannon, 650 Fifth Ave., Fort Worth 4, Texas.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7 P.M. at University Hospital.

University of Wisconsin Radiological Conference
Secretary, Dr. E. A. Pohle, 1300 University Ave., Madison, Wis. Meets first and third Thursdays 4:00 to 5:00 P.M., September to May inclusive. Room 203, Service Memorial Institute, 426 N. Charter St., Madison.

Utah Radiological Conference
Secretary, Dr. Henry H. Lerner, School of Medicine, University of Utah, Salt Lake City 1. Meets 1st and 3rd Thursdays monthly from 7:30 to 10 P.M., Salt Lake County General Hospital, September to June.

Utah State Radiological Society
Secretary, Dr. M. Lowry Allen, Judge Bldg., Salt Lake City 1, Utah. Meets third Wednesday in September, November, January, March and May.

Virginia Radiological Society
Secretary, Dr. P. B. Parsons, Norfolk General Hospital, Norfolk, Va. Meets annually in October.

Washington State Radiological Society
Secretary, Dr. Homer V. Hartzell, 310 Stimson Bldg., Seattle 1, Wash. Meets fourth Monday each month, October through May, College Club, Seattle.

X-Ray Study Club of San Francisco
Secretary, Dr. Ivan J. Miller, 2000 Van Ness Ave. Meets monthly on third Thursday at 7:45 P.M., first six months of year at Lane Hall, Stanford University Hospital, and second six months at Toland Hall, University of California Hospital.

Cuba

Sociedad de Radiología y Fisioterapia de Cuba
President, Dr. J. Manuel Viamonte, Hospital Mercedes, Habana, Cuba. Meets monthly in Habana.

Mexico

Sociedad Mexicana de Radiologia y Fisioterapia
General Secretary, Dr. D. P. Cossio, Marsella No. 11, Mexico, D. F. Meets first Monday of each month.

British Empire

British Institute of Radiology Incorporated with the Roentgen Society
Medical Members' meeting held monthly on third Friday at 2:30 P.M. and Ordinary Meeting at same time on following Saturday, October to May, 32 Welbeck St., London, W.1.

Faculty of Radiologists
Secretary, Dr. M. H. Jupe, 23 Welbeck St., London, W.1 England.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 1 Wimpole St., London.

Canadian Association of Radiologists
Honorary Secretary, Dr. E. M. Crawford, 2100 Marlowe Ave., Montreal 28, Que. Meetings January and June.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Francaise d'Electrologie et de Radiologie Médicales
Secretary, Dr. Origéne Dufresne, 4120 Ontario St., East, Montreal, P. Q.

Australian and New Zealand Association of Radiologists
Honorary Secretary, Dr. Alan R. Colwell, 135 Macquarie St., Sydney, N.S.W.
Honorary Secretaries, State Branches:
New South Wales, Dr. E. W. Frecker, 135 Macquarie St., Sydney.
Victoria, Dr. T. L. Tyrer, 3 Lockerbie Court, East St. Kilda.
Queensland, Dr. J. Adam, 131 Wickham Terrace, Brisbane.
South Australia, Dr. B. C. Smeaton, 178 North Terrace, Adelaide.
Western Australia, Dr. A. M. Nelson, 179-B St. Georges Terrace, Perth.
New Zealand, Dr. E. G. Lynch, 12 Bolton St., Wellington.

South America

Sociedad Argentina de Radiologia
Secretary, Dr. Guido Gotta, Buenos Aires, Argentina. Meetings are held monthly.

Sociedade Brasileira de Radiologia Medica
Secretary, Dr. Nicola Caminha, Av. Mem de Sa, Rio de Janeiro, Brazil. Meets monthly, except during January, February and March.

Sociedade Brasileira de Radioterapia
Secretary, Dr. Andrelino Amaral, Av. Brigadeiro Luiz Antonio, 644, São Paulo, Brazil. Meets monthly on second Tuesday at 9 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Peruana de Radiologia
Secretary, Dr. Julio Bedoya Paredes, Apartado, 2306 Lima, Peru. Meetings held monthly except during January, February and March, at the Asociación Médica Peruana "Daniel A. Carrión," Villalta, 218, Lima.

Continental Europe

Société Belge de Radiologie
General Secretary, Dr. S. Masy, 111 Avenue des Alliés, Louvain, Belgium. Meets monthly, second Sunday at Maison des Médecins, Brussels.

Ceskoslovenská společnost pro röntgenologii a radiologii v Praze
Secretary, Dr. Roman Bláha, Praha XII, stát. nemocnice, Czechoslovakia. Meets monthly except during July, August, and September. Annual general meeting.

Polish Society of Radiology
Secretary, Dr. L. Zgliczynski, 59 Nowogrodzka St., Warsaw, Poland. Next meeting May 13 and 14, 1948.

Gdansk Section, Polish Society of Radiology
Secretary, Dr. A. Smigielska, Akademia Lekarska, Gdansk. Meets monthly last Sunday at 10.30, X-Ray Dept., Akademia Gdansk.

Warsaw Section, Polish Society of Radiology
Secretary, Dr. L. Zgliczynski, 59 Nowogrodzka St., Warsaw, Poland. Meets monthly.

Societatea Romana de Radiologie si Electrologie
Secretary, Dr. Oscar Meller, Str. Banual Mărăcine, 30, S. I., Bucuresti, Roumania. Meets second Monday in every month with the exception of July and August.

All-Russian Roentgen Ray Association, Leningrad. USSR in the State Institute of Roentgenology and Radiology, 6 Roentgen St.
Secretaries, Drs. S. A. Reinberg and S. G. Simonson. Meets annually.

Leningrad Roentgen Ray Society
Secretaries, Drs. S. G. Simonson and G. A. Gusterin. Meets monthly, first Monday at 8 o'clock, State Institute of Roentgenology and Radiology, Leningrad.

Moscow Roentgen Ray Society
Secretaries, Drs. L. L. Holst, A. W. Ssamygin and S. T. Konobejevsky. Meets monthly, first Monday, 8 P.M.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

Sociedad Espanola de Radiologia y Electrologia
Secretary, Dr. J. Martin-Crespo, Fuencarral, 7. Madrid, Spain. Meets monthly in Madrid.

Schweizerische Röntgen-Gesellschaft (Société Suisse de Radiologie)
Presidents, Dr. H. E. Walther, Gloriastr. 14, Zürich, Switzerland. Annual meeting, on the Bürgenstock, near Lucerne, May 22 and 23, 1948.

SIXTH INTERNATIONAL CONGRESS OF RADIOLOGY

Approval has been given by the Executive Committee for the Sixth International Congress of Radiology to be held in London in the summer of 1950, under the Presidency of Dr. Ralston Paterson of Manchester, England. The officers for the Congress are as follows:

President	Dr. Ralston Paterson
President Emeritus	Dr. A. E. Barclay
Vice-Presidents	Dr. S. Cochrane Shanks
	Prof. B. W. Windeyer
	Prof. W. V. Mayneord
	Dr. F. Gordon Spear
Treasurer	Dr. H. Graham Hodgson
Secretary-General	Dr. J. W. McLaren

All recognized radiological societies are being asked to supply a list of their members, and full details will be sent to each radiologist and published as soon as possible. An office for the Congress has been established at 45 Lincoln's Inn Fields, London, W. C. 2, England.

J. W. McLaren
Secretary-General

COURSE IN CARDIAC ROENTGENOLOGY

A course in Cardiac Roentgenology for radiologists will be offered at the Center for Continuation Study at the University of Minnesota, October 25–30, inclusive, 1948. The participating faculty will be Dr. Richard Bing of Baltimore, Maryland, Dr. Fred J. Hodges of Ann Arbor, Michigan, Dr. Merrill C. Sosman of Boston, Massachusetts, and Dr. Marcy L. Sussman of New York, New York. In addition, the graduate faculty of the Mayo Foundation and the University of Minnesota will participate.

Further information and applications can be obtained from Dr. George Aagaard, Director of Post-Graduate Medical Instruction, University of Minnesota, Minneapolis, Minnesota.

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY

The Rocky Mountain Radiological Society will meet in Salt Lake City, Utah, on August 12, 13 and 14, 1948, at the Hotel Utah. An excellent program is in process of preparation and it is hoped that as many radiologists as possible will plan to attend. The program will be published in the July issue of the Journal.

GEORGIA RADIOLOGICAL SOCIETY

At the annual meeting of the Georgia Radiological Society the following officers were elected for the coming year: *President*, Dr. H. H. McGee, Savannah, Georgia; *Vice-President*, Dr. Max Mass, Macon, Georgia; *Secretary-Treasurer*, Dr. Robert Drane, Savannah, Georgia. The annual meeting of the Society was held in conjunction with the Medical Association of Georgia in Atlanta.

KANSAS RADIOLOGICAL SOCIETY

At a recent organization meeting the Kansas Radiological Society was formed. The Secretary-Treasurer is Dr. Anthony F. Rossitto, Wichita Hospital, Wichita, Kansas. Meetings will be held annually with the Kansas State Medical Society.

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ROENTGEN DIAGNOSIS

HEAD

JAEGER, RUDOLPH, and FORBES, ROY P. Bilateral congenital arteriovenous communications (aneurysm) of the cerebral vessels. *Arch. Neurol. & Psychiat.*, June, 1946, *55*, 591–599.

Cerebral arteriovenous aneurysms have frequently been recorded in the literature. However, prior to a previous brief account of this case, the occurrence of bilateral cerebral arteriovenous communications had not been reported. The authors now report their case in detail.

A male infant weighing 9½ lb. was delivered with difficulty by forceps. Following initial normal breathing, respiratory failure developed and was overcome with difficulty. At birth, the head was enlarged and the bones were thicker than normal. Some prominence of the veins of the head was noted during infancy. At eight months, following influenza, he developed epistaxis and fainting spells. A cardiac murmur was discovered and the heart began to enlarge. This pattern, respiratory disease and epistaxis, was repeated often during the following two years. At twenty-seven months, a loud bruit was discovered in the neck just below the left ear. Upon reaching the age of three, the epistaxis had gradually decreased to be replaced by intermittent headaches and vomiting which occurred at intervals of several days to three weeks. He died during his fifth year following a retrogressive course which included loss of articulate speech and locomotion. Approximately six weeks before death the left common carotid artery was ligated.

The classification of arteriovenous aneurysms as traumatic, infectious, and congenital is suggested to indicate their etiology. The traumatic variety is produced in cases in which a penetrating wound produces injury to large arteries and veins which lie in close approximation. Inflammation may directly erode a vessel or perforation of a mycotic aneurysm may establish an arteriovenous communication. A quite common cause, however, is failure in the development of the capillary bed which is normally interposed between the arterial and venous system. As might be expected, in the last type, there are many large anastomosing channels between the arterial tree and venous return.

Several excellent anatomical plates are reproduced to illustrate the vascular abnormalities in the case presented. The interesting features and the congenital embryological basis is discussed —*Robert N. Byrne.*

GRANT, FRANCIS C. Intracranial meningiomas, surgical results. *Surg., Gynec. & Obst.*, Oct., 1947, *85*, 419–431.

Between January 1, 1936, and January 1, 1947, one thousand and one brain tumors were verified in the Neurosurgical Clinics of the

University and Postgraduate Hospitals of the University of Pennsylvania. Of these, 149, or 14.8 per cent, were meningiomas.

Vital Statistics. Of these 149 patients, 92 were females; 57, males. Four of the males and 2 of the females were Negroes. The youngest patient was two years; the oldest, seventy-six. The average age at operation was forty-three plus years for the women, forty-three minus years for the men. The average duration of symptoms prior to operation approximates $2\frac{3}{4}$ years. Injury appears to have been a factor in 14 cases, all vault tumors.

Position of the Tumor

Bilateral frontal	13
Sphenoid ridge	17
Frontotemporal	13
Suprasellar	7
Gasserian ganglion	3
Cerebellar	11
Frontal	37
Frontoparietal	9
Temporal	10
Parietal	11
Parieto-occipital	12
Intraventricular	3

As was to be expected, the more closely the tumor lay to the carotid vessels, olfactory groove, suprasellar area, sphenoid ridge, and to the base of the skull, gasserian ganglion and posterior fossa, the higher the mortality and the less the chance of a complete removal.

Diagnosis. In 33 of these 149 verified meningiomas, localization of the lesion was impossible on the basis of careful and painstaking neurologic studies and routine roentgen examinations. The plain films of the skull were entirely negative in 48 cases. In 81 cases the routine skull examination strongly suggested the position of the lesion and in 38 of these, not only was the position of the lesion correctly estimated but a positive diagnosis of meningioma was reached. In 20 cases the presence of a mass lesion was definite on the basis of the pineal shift. In the 48 cases in which an initial study of the plain skull films was reported negative, re-study of the films after the position of the tumor was known, showed suggestively positive findings in 14.

Ventriculograms were performed in 61 cases with 2 missed diagnoses both because of insufficient air. In 20 instances an encephalogram was performed localizing the tumor accurately in 16 cases.

Conclusions. Diagnosis and localization of intracranial meningiomas can be correctly made in 98 per cent of cases.

These tumors are benign. Complete removal, with dural attachment precludes recurrence. The surgeon should always keep this fact in mind. His problem is total extirpation of the tumor with minimum damage to adjacent brain areas thus reducing neurologic sequelae.—*Mary Frances Vastine.*

Speigel, Joshua I. Cerebral schistosomiasis; report of a case with surgical removal of an intracerebral mass of schistosomal ova. *J. Neurosurg.*, Jan., 1947, *4*, 72–80.

A large number of fluke infestations have been encountered in the American troops stationed in the islands of the southwest Pacific and in Japan, Formosa, the Celebes, and Burma In the case reported a mass of schistosomal ova was found, surgically, in the brain. The patient, a white male, aged twenty-two, had been perfectly well until he had a severe grand mal seizure, followed by others and accompanied by persistent headache, diplopia and falling to the right when walking. During the following weeks the unsteadiness became so severe that walking was impossible and there developed slurring of his speech.

While a patient at Mayo General Hospital approximately two months later, roentgenograms of the skull revealed sharpening and erosion of both anterior clinoids, most marked on the right with some reduction in size of the latter. A ventriculogram revealed a shift of the entire ventricular system to the left, most marked anteriorly. Accordingly, a large right frontotemporal osteoplastic craniotomy was performed. Many small masses, varying in size from that of a wheat seed to that of a walnut, were removed from beneath the cortex. Frozen section revealed many characteristics of a granuloma on a parasitic basis. The patient made an uneventful recovery. Following operation, stool examinations revealed the presence of schistosomal ova.

The pathological picture of cerebral schistosomiasis resembles that of schistosomiasis in any other part of the body, and the neurological picture of infestation of the brain and spinal cord does not differ in any way from other infections in the central nervous system except that in cerebral involvements there appears to be a tendency to convulsive seizures, confusion and disorientation. If the ova exist as a space-

occupying lesion in the brain it appears from the previous reports and from this case that excellent results may be expected if the mass is surgically removed and a course of antimony administered.—*K. K. Latteier.*

GOVONS, SIDNEY R., and GRANT, FRANCIS C. Arteriographic visualization of cerebrovascular lesions. *Arch. Neurol. & Psychiat.*, June, 1946, *55*, 600–618.

Cerebral angiography as a method of localizing intracranial lesions was first introduced by Egas Moniz in 1927. He strongly advocated the use of his method for the localization of cerebral neoplasms, but for the present air insufflation remains the procedure of choice. There is agreement, however, that cerebral angiography is a useful technique for the localization of certain vascular lesions, namely, intracranial aneurysm, angiomatous malformations, occlusion of the internal carotid artery and traumatic arteriovenous aneurysm.

Briefly, the technique employed consists of exposure of the common or internal carotid artery under local procaine anesthesia; 10 to 15 cc. of colloid suspension of thorium dioxide is rapidly injected. The first film is made when 10 cc. has been injected and the second, five seconds later.

The course of the internal carotid artery is described. It is pointed out that in 69 per cent of cases a double carotid siphon will be present. The authors prefer to inject the common carotid artery. With experience the common and internal carotid circulations are easily distinguished and as the opaque suspension enters the internal carotid circulation more readily, failure to visualize this distribution directs attention to possible occlusion.

The incidence of intracranial aneurysm ranges from 0.5 to 1.6 per cent of routine postmortem examinations of the head. Etiologically these lesions may be classified as mycotic, arteriosclerotic and congenital. The mycotic type is rare and the arteriosclerotic uncommon. Syphilis plays little or no role. The majority of intracranial aneurysms occur in the anterior portion of the circle of Willis. The outstanding manifestations are sudden headache, neck stiffness, severe pain over the eye or forehead and possible loss of consciousness. As a subarachnoid hemorrhage is the precipitating cause, its extent will determine the clinical picture.

Angiomatous malformations comprised about 1 per cent of Cushing and Bailey's (1928) series of verified intracranial tumors. Dandy estimated the incidence as 0.5 to 1.0 per cent of the cases in clinics in which neurological material is concentrated. They may occur anywhere in the brain but a large proportion are found in the distribution of the middle cerebral artery. As a rule, the lesion remains quiescent until adult life. The presenting symptom in about one-half the patients is epileptiform seizure which may be preceded by transient sensory or motor paralysis. Less frequently intracranial hemorrhage with or without paralytic phenomena may be the initial manifestation. A few patients may first complain of headache. Usually there is no choking of the discs or head bruit. Roentgenograms generally show accentuated vascular markings; occasionally intracranial calcification is present.

Thrombosis of the carotid artery as a source of neurologic disturbance is frequently ignored, both in clinical and pathological studies. The condition is seen in young adults as well as the elderly. The most frequent associated lesions are aortic sclerosis or pressure from an aortic aneurysm. Obliterating syphilitic arteritis without aneurysm; embolism, and non-syphilitic arteritis have been reported in a few instances. The clinical picture will be varied and depend upon the collateral circulation. A frequent history is that of transient attacks of hemiparesis progressing to permanent hemiplegia with or without sensory paralysis or aphasia. Roentgenograms of the skull are usually normal, occasionally calcification of the internal carotid artery may be seen.

The creation of a fistula between the carotid artery and the cavernous sinus is commonly the result of cranial trauma, especially when a basilar fracture of the sphenoid bone occurs. The aneurysm is usually unilateral, rarely bilateral, and the symptoms may progress rapidly or slowly. The most frequent symptoms are bruit, headache, and unilateral pulsating exophalmos, with diplopia, chemosis and visual disturbances.

Case histories and roentgenograms are presented to illustrate the described lesions.—*Robert N. Byrne.*

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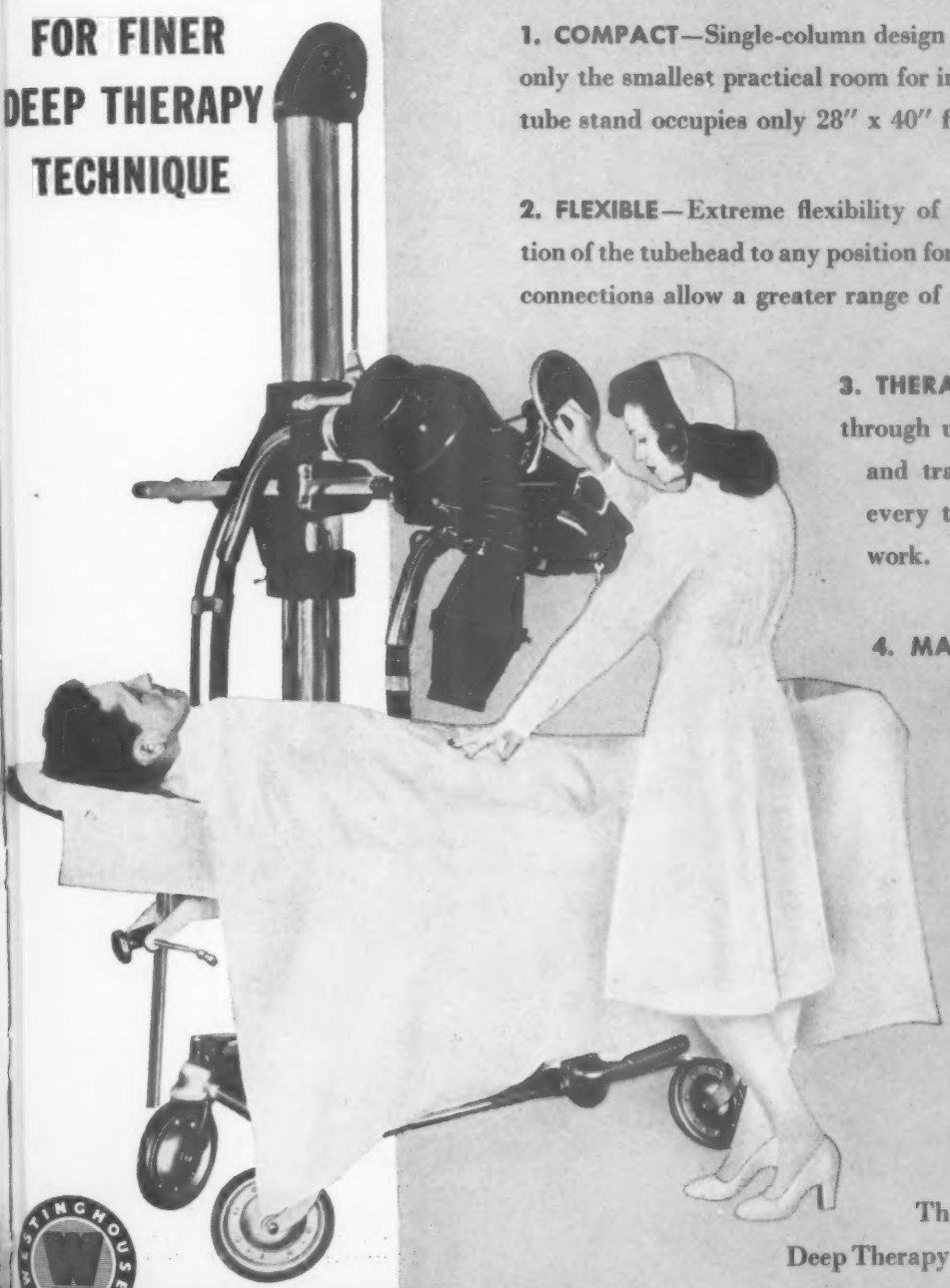

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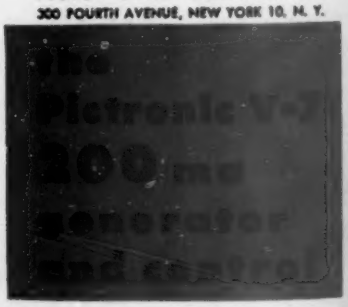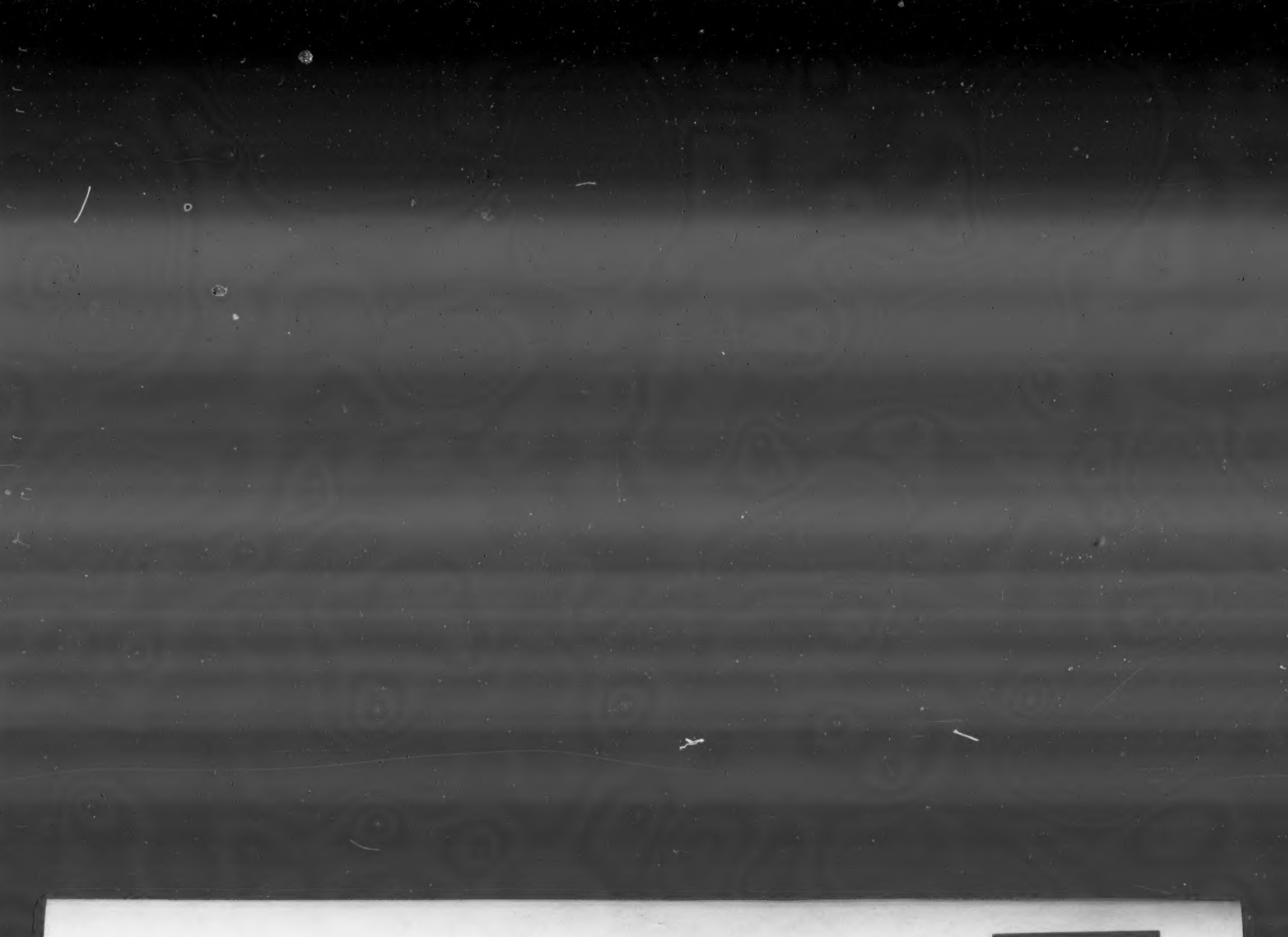
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